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Notes on Acute Rheumatic Disease of the Heart[1]

By William S. Thayer

From the Department of Medicine of the Johns Hopkins Hospital and University

Among the cases of acute or subacute endocarditis coming to necropsy within the last thirty-five years at the Johns Hopkins Hospital there were twenty-five which appeared to be of indisputably pure rheumatic origin without demonstrable complicating bacterial septicæmia.[2]

Having brought together this group for the sake of comparison with the bacterial endocarditides I am tempted to present a brief analysis of the series which is not devoid of interest.

Age. The age incidence ranged from six to forty-seven. Seventy-six per cent of the cases occurred in the first two decades of life; 88 per cent in the first three.

While death from the late results of rheumatic heart disease is common in later life, fatal acute and subacute rheumatic endocarditis appear to prevail in the early years. Rheumatic fever is essentially a disease of childhood and youth.

Sex. Seventeen of our cases were males; 8 were females.

Race. Seventeen were white; 8, coloured.

Pre-existing valvular disease was the rule, even in patients so young as those in our series. Evidences, clinical and anatomical, of chronic valvular disease were present in 84 per cent of our cases.

Portal of entry and manner of onset. In the absence of definite knowledge as to the infectious agent in acute rheumatic heart disease, it is very difficult to speak of the portal of entry. There is, however, a good deal in the history of the disease to suggest a possible relation between acute rheumatic fever and local foci of infection, notably disease of the tonsillar and pharyngeal adenoid tissue and of the teeth.

In 68 per cent of our patients *infected tonsils or pharyngeal adenoids were noted.* Five of the 25 patients showed *peridental infection.*

There were no other notable indications as to the portal of entry save that once the acute symptoms seemed to follow an infected finger.

Arthritis. In 72 per cent of the cases there was a polyarthritis during

[1] Remarks made before the Medical Section of the American Medical Association at Chicago, Ill., June, 1924.

[2] In one instance with a terminal broncho-pneumonia there were a few microscopical abscesses in the heart muscle. As the blood cultures remained sterile and the heart muscle showed characteristic Aschoff bodies, the case was retained in the series.

the attack, and in an equal number there was a history of *preceding* arthritis.

Every patient had had arthritis during the attack or previously save one, a child of seven with a mild acute chorea and grave myocardial changes dating from a previous attack.

Manner of onset. In those cases which did not begin with a polyarthritis—and in some of those which did—the onset was usually rather vague and indefinite, associated with the general symptoms of an acute infection. In a surprisingly large proportion of the cases the arthritic symptoms were slight. The disease was one of the heart rather than of the joints. Especially significant was the presence of unaccountably persistent fever in association with chorea or mild atypical arthritis.

The *fever* was continuous in 76 per cent of the cases, often with slight or more pronounced remissions, not notable for their regularity.

In somewhat under one-quarter of the cases the fever was irregularly intermittent. In three it was slight with periods of normal and subnormal temperature.

In 44 per cent of the cases temperatures above 104° were recorded. In 16 per cent the temperature remained below 102.5°F.

Chills and chilly sensations were complained of in but one case and then at the onset. This is in sharp contrast to that which is observed in some of the acute bacterial endocarditides.

Petechiae were not observed in a single one of these twenty-five cases.

Splenic enlargement was not striking; the spleen was felt but once.

Embolic phenomena were not recognized clinically. Renal infarctions were found post mortem in 3 cases. In one of these the seat of origin of the embolus was probably an intraventricular thrombus; in another a thrombus in the left auricular appendage. In the third, the cause of infarction was not apparent. There was no obvious source for an embolus and it may have been an autochthonous thrombus. Thrombi in the auricular appendages were noted in 5 cases, 20 per cent. In none of these, so far as could be made out from the history, was there auricular fibrillation. In none were there pulmonary infarctions.

Pulmonary infarctions were, however, observed in 3 cases, in one of which there was auricular fibrillation.

Cerebral embolism, so common in subacute bacterial endocarditis, was not observed.

Clubbed fingers were noted in two of the 25 cases—a boy of eight with chronic valvular disease of at least two years' duration; a man with chronic valvular and muscular disease.

Albuminuria was the rule, occurring in 18, 81.9 per cent, of 22 cases in which notes were made.

Acute nephritis was noted pathologically in but one instance; a sharp contrast to that which is seen in bacterial endocarditis.

Red blood corpuscles were observed in the urinary sediment but once, and then on the day before death in a man of twenty-six with a terminal pneumonia.

The *blood* showed evidences of a moderate secondary anæmia. There was, however, in almost every case, a pronounced leucocytosis, averaging between 15,895 and 21,308.

Records under 8000 were obtained in but 3 cases; while in 20 of the 22 cases there were leucocyte counts of above 10,000.

The highest leucocyte count was 37,000.

Acute and subacute rheumatic heart disease was characterized, then, by a rather pronounced increase in colourless corpuscles. Morphologically, this was a characteristic polymorphonuclear neutrophilic leucocytosis, the polymorphonuclear percentage in 9 cases averaging 81.4 per cent for a leucocytosis of 14,231.

Cause of death. Death occurred almost invariably with myocardial insufficiency and dilatation of the heart.

Terminal pneumonia occurred in 10 cases.

The *duration* of the process was very difficult to determine, so difficult, indeed, that in 5 of the 25 cases it was unjustifiable even to record a guess. Among the other 20, the duration appeared to range from two weeks to several months.

Acute pericarditis, sero-fibrinous or fibrinous, occurred in 17 cases, 68 per cent. Once the effusion was hæmorrhagic. In none of the series were there large effusions.

Acute or chronic pericarditis was present in every case but one, 96 per cent.

Pericarditis then, was the rule in acute rheumatic heart disease, justifying the French term "endo-péricardite."

Acute myocarditis—and this is a characteristic feature of acute rheumatic heart disease—is equally frequent, occurring in 22 (92.5 per cent) of 24 cases in which sections of the heart muscle were available for study. Once there were a few microscopical myocardial abscesses which, in all probability, were dependent on a late secondary infection—there was a terminal broncho-pneumonia—although blood cultures had been negative. There was in this case, however, a characteristic rheumatic myocarditis as well. The essential myocardial lesions were the peculiar and distinctive perivascular foci of cellular infiltration and subsequent scarring described by Aschoff and recently studied by Swift.[3]

In 21 of 24 cases (87.5 per cent) characteristic Aschoff bodies were found in the heart muscle. In one case sections of the heart muscle were unavailable.

Chronic fibroid myocardial changes were found in 14 (58.3 per cent) of the cases.

When one considers that 76 per cent of these patients were in the first two decades of life, 88 per cent in the first three, the significance of this observation is readily appreciable. It is quite in accord with the clinical history of preëxisting valvular disease in 84 per cent.

Either acute or chronic myocardial changes occurred in all of the 24 cases in which the heart muscle was available for examination.

The character of the valvular lesions in rheumatic endocarditis need not be emphasized here. In all instances they were small verrucose nodules distributed along the free edge of the valves or along their lines of contact. In one characteristic case there was, in addition, an interesting area of necrosis on the under surface of a mitral curtain—a subacute process. There were

[3] Swift, H. F.: The pathogenesis of rheumatic fever. Jour. Exp. Med., 1924, xxix, 497.

Aschoff bodies in the heart muscle and the blood was sterile.

Anatomical distribution of the endocardial lesions. The lesions were confined to the left side of the heart in 14, or 58 per cent, of the cases; to the right, in 1 case; they were found on both sides in 10, or 40 per cent.

The mitral valve was implicated with greatest frequency, in 88 per cent; the aortic in 80 per cent; the tricuspid in 44 per cent; the pulmonic but once. This frequency of tricuspid involvement has been noted by others, notably by Libman.[4]

Pre-existing valvular disease, as has been said, was observed in 84 per cent.

Among the individual affected valves chronic changes were noted in 62.9 per cent.

Mural endocarditis. As is well known, subacute streptococcal endocarditis affects the wall of the left auricle with notable frequency. So striking is this phenomenon that we have been in the habit of regarding puckered, scarred thickened areas in the endocardium of the left auricle as suggestive of healed subacute streptococcal infection. MacCallum,[5] however, has recently pointed out that such patches in the left auricle are not uncommon in rheumatic endocarditis, representing the reaction of the endocardium over areas of cellular infiltration and scarring in the wall of the auricle. In acute cases the subjacent tissue is studded with Aschoff bodies.

In 5 of our cases there were such puckered, thickened patches in the left auricle which were the seat of an acute endocardial proliferation; sometimes there were verrucosities; sometimes the affected area was covered by a thin fibrinous layer.

Going back over our records I found that in 5 more of this group of cases wrinkled, rough, opaque or scarred areas in the auricular wall were described in the routine necropsy note.

Acute mural endocarditis of the left auricle was noted, then, in 20 per cent of our cases, while evidence of preexisting lesions was clear in 5 more. In other words, acute or chronic mural endocarditis in the left auricle was present in 40 per cent of the series.

Sero-fibrinous pleurisy was observed in 10 cases (40 per cent); chronic adhesive pleurisy, once.

Pneumonia or broncho-pneumonia occurred 11 times, 44 per cent; once, broncho-pneumonia occurred during life but cleared up before death. In the other 10 instances the pneumonia was terminal.

Vascular thromboses, apart from those on the valves or in auricular appendages, occurred but once.

Meningitis (tuberculous) occurred once.

Focal suppurative processes, so common in some forms of bacterial endocarditis, were observed but once, in a case complicated by a terminal broncho-pneumonia—small abscesses of the myocardium—clearly a terminal infection. Once there was a complicating tuberculosis.

Bacteriological studies were negative in every case in which they were made. Cultures from the blood during life or at necropsy were made in 18 of the 25 cases. They remained sterile invariably. In the other 7 cases although no cultures were made, bacterioscopical

[4] Tr. Assn. Am. Phys., Philadelphia, 1922, xxxviii, 237.

[5] Johns Hopkins Hosp. Bull., 1924, xxxv, 329.

examinations at the necropsy revealed nothing.

Several characteristic instances of acute rheumatic endocarditis were omitted from this series because of terminal streptococcus septicæmia.

SUMMARY

In this series of cases, acute rheumatic heart disease prevailed in early youth.

While the ætiological element was not apparent, the sequence of the disease on acute tonsillar or nasopharyngeal infections was striking.

The onset was often associated with outspoken acute articular rheumatism or with chorea. In other instances, however, the arthritis was mild or even absent, or the chorea insignificant. It is obvious, as Swift has pointed out[6] that arthritis and chorea (encephalitis) are but individual focal manifestations of a general process the gravest effects of which are often exercised on the heart which is probably affected from the outset, in a large proportion of cases.

In cases in which the arthritis or the nervous symptoms were slight, cardiac involvement, in the absence of an obvious pericarditis, was revealed often only by unaccountable or persistent fever and a pronounced leucocytosis.

The earlier symptoms of acute rheumatic heart affection were not caused by the endocarditis which, at this stage, was a mere incident of the disease. Mitral insufficiency in the early stages of an acute rheumatic heart disease is probably in most instances dependent on muscular relaxation due to myocardial changes, the earlier endocarditic lesions being usually incapable of producing a murmur. Only later, with convalescence and scarring, are the endocardial changes sufficient to produce essential valvular insufficiencies or stenoses.

The character of the fever in acute rheumatic heart disease varied greatly. In some cases, high and continued, in others it was insignificant, remittent or intermittent.

Embolic phenomena were absent.

Albuminuria was the rule, but red blood corpuscles in the urinary sediment, so commonly found in subacute bacterial endocarditis, were not observed in rheumatic heart disease.

The fatal issue depended, in all of our cases, on myocardial insufficiency, although associated terminal pneumonia was not uncommon.

These 25 cases of rheumatic heart disease were, almost always, a true pancarditis. Endo-, myo-, and pericarditis occurred with almost equal frequency.

The one characteristic lesion appeared to be the perivascular Aschoff bodies which were found not only in the heart muscle but in the affected pericardium, in the auricular wall and even, on occasions, in the affected valves. The almost universal presence of Aschoff bodies in this series is striking.

The myocardial and pericardial changes appeared to be the gravest features of acute rheumatic heart disease and led, of themselves, to a fatal issue while the endocarditis was yet in its infancy.

The endocarditis affected the mitral and aortic valves in an overwhelm-

[6] Jour. Exp. Med., 1924, xxxix, 497–508.

ing majority of cases, especially the former; but the tricuspid valve was implicated in 44 per cent.

The anatomical character of the endocarditis, the small verrucosities on the free edges of the valves and along the lines of contact need not be emphasized.

Mural endocarditis occurring in the left auricle was not infrequent. This was met with as patches, which in their acute stages were covered by a delicate layer of fibrin or by actual verrucosities; later they were represented by opaque, wrinkled, scarred-looking areas. During the acute stages these were found to overlie foci of cellular infiltration in the auricular wall, containing numerous Aschoff bodies.

In conclusion, the rheumatic origin of the manifestations of acute heart disease must naturally be regarded as probable when these are associated with polyarthritis or chorea.

When, however, neither arthritis nor chorea is evident, a rheumatic carditis may be suspected from the youth of the patient, the history of previous arthritis or chorea, the evidences of tonsillitis, negative blood cultures, the frequency of sero-fibrinous pericarditis, relatively rare in acute and subacute bacterial endocarditis, the pronounced leucocytosis and the absence of petechiae, of evidence of splenic enlargement, embolic phenomena or of blood in the urine.

Especially significant, however, are electrocardiographic changes[7] or the early onset of failure of the heart muscle, which reveal the presence of myocardial involvement, much more common in rheumatic disease than in other cardiac affections.

[7] Swift, H. F., and Cohn, A. E.: Electrocardiograph evidence of myocardial involvement in rheumatic fever. Jour. Exp. Med., 1924, xxxix, 1–33.

Section of the Sensory Root of the Trigeminal Nerve at the Pons

Preliminary Report of the Operative Procedure

By Walter E. Dandy

From the Surgical Clinic of the Johns Hopkins Hospital and University

In TWO patients afflicted with tic douloureux the sensory root of the trigeminal nerve was sectioned alongside the pons. The approach to the nerve in this region is through the posterior cranial fossa; in all other operative procedures the sensory root is approached from the middle cranial fossa. Except for the fact that the bony defect is extended laterally and above, a more or less routine unilateral cerebellar exposure is made. The dura is incised almost to the lateral and sigmoid sinuses, both of which are carefully avoided. To facilitate still further a deep exposure in the posterior cranial fossa, much room can be obtained by liberating all the fluid contained in the cisterna magna. This is done by puncturing the membrane. In one case, even more room was obtained by a preliminary intravenous injection of Weed's hypertonic salt solution.

The cerebellar lobe is elevated with a narrow spatula which is gradually pushed mesially under the cerebellum and along the angle formed by the tentorium cerebelli and the posterior surface of the petrous temporal bone, until the brain-stem is reached. The acoustic and facial nerves entering the internal auditory meatus are passed *en route* but are not disturbed. The characteristic position of the trigeminal nerve at the apex of the petrous temporal bone, and piercing the tentorium, makes it not difficult of detection. The brain-stem including this part of the trigeminal nerve is surrounded by the arachnoid membrane and must be opened before the nerve can be divided. In one case the membrane was transparent, the nerve being easily visible through it. In the other, the membrane was so opaque and thick that the nerve could be seen only when the membrane was opened. A fairly large vein lying adjacent to the nerve enters the superior petrosal sinus and must be carefully avoided. In one case another small vein paralleled the sensory root and had to be divided between Cushing "clips" before the nerve could be sectioned. A small hook was passed around the sensory root, which was then gently pulled and divided. In both cases the motor root was uninjured and could be seen intact through the hiatus in the severed sensory root and lying parallel to, behind, and along its superior border.

In presenting this procedure, it is

realized that the operations now in use for section of the sensory root through the middle cranial fossa are practically devoid of mortality in the hands of competent surgeons. Although the recovery of these patients was uneventful, the material is too limited to suggest that this operation is either equal or superior to other procedures. Its advantages are: (1) the ease of the approach to the sensory root, due largely to the bloodless intracranial course; after entering the dura a free space without vascular crossings extends directly to the brain-stem; (2) the seemingly easier preservation of the motor root.

Its greatest disadvantage would appear to be that the operation is intradural and that for this reason the effects of trauma from any undue retraction of the cerebellum and the difficulties incident to any unexpected bleeding would be serious. Whether those potential dangers prove to be actually greater than in other operations remains to be seen.

Studies on the Pathological Histology of Experimental Carbon Tetrachloride Poisoning[1,2]

By George H. Gardner, R. C. Grove, R. K. Gustafson, E. D. Maire, M. J. Thompson, H. S. Wells and Paul D. Lamson

From the Departments of Pathology and Pharmacology, the Johns Hopkins University

INTRODUCTION

As a result of Hall's original observations (2), in 1921, on the efficacy of CCl_4 in removing hookworms from dogs, over a million (3) human cases of hookworm disease have been treated successfully with this drug. It is generally accepted that disagreeable and dangerous symptoms are much less conspicuous after the administration of CCl_4 than after any other anthelmintic so far used to remove hookworms; however, a few cases of severe poisoning and several deaths have occurred. Pessoa and Meyer (4) had found that, after oral administration of CCl_4 to dogs, liver necroses occur which are comparable to those observed after poisoning with chloroform, a closely allied substance, chemically; Lambert (5) reported central necrosis of the liver in a fatal human case; while Meyer and Pessoa (6) found kidney changes in dogs. Considerable discussion arose as to the cause of the symptoms, deaths and pathological changes—whether they were due to CCl_4 itself or to impurities in the commercial preparations. Furthermore, the question of the advisability of continuing treatment with CCl_4 was raised.

Because of its great economic value (hundreds of thousands of cases are being cured of hook worm disease yearly), we were asked by the International Health Board to undertake an investigation on the toxicity and pharmacology of CCl_4 as well as on the pathological changes following its administration. Results of pharmacological experiments have been reported (1) under headings similar to those used in this paper. Since studies herein reported are based on some 240 animals used, for the most part, previously for pharmacological experiments, certain points have been emphasized more than would have been the case in a series of purely pathological experiments.

METHODS

The investigations have been carried out with chemically pure (1) CCl_4

[1] This is our second report of studies on CCl_4 (1) undertaken at the request of and supported by the International Health Board.

[2] Received for publication August 8, 1924.

especially prepared for us by the Eastman Kodak Company, through the kindness of Dr. H. T. Clarke.

Dogs were selected as the experimental animals. They were observed at least one day before being used and then only apparently healthy adults of medium size were chosen. Later, in a comparative study, puppies and rabbits were used. No effort was made to determine the presence of hookworms in any of these animals, nor were stools examined after dosing to determine the anthelmintic effectiveness of CCl_4.

In beginning these studies the dogs autopsied were those which *died* after receiving CCl_4. Later, appreciating the changes which occur, we were desirous of observing their development and healing. To this end animals were killed at specified times, by intracardiac injections either of 1 per cent potassium cyanide or a saturated solution of magnesium sulphate. At autopsy, tissue from the thymus, lungs, heart, spleen, pancreas, mesenteric lymph glands, stomach, intestines, liver, gall-bladder, adrenal, kidneys, urinary bladder, prostate or uterus, testes or ovaries, aorta, bone-marrow, thyroid and parathyroids was fixed in (*a*) Helly's fluid (7) and (*b*) 10 per cent formalin, for histological study. The entire brain with the hypophysis was fixed in 10 per cent formalin.

Hematoxylin and eosin stained sections cut from paraffine have been used for routine study. Nile blue sulphate, Scharlach R and Sudan III have been employed as fat stains; for iron, the Prussian blue reaction with potassium ferrocyanide has been utilized.

CONTROL ANIMALS

Five apparently healthy adult dogs and 3 puppies were killed as controls. In the intestines of each there were either tapeworms or roundworms; 2 of the adults were also infested by hookworms. Microscopical examination shows a kidney change which we consider abnormal; in the cortex there are foci of round and plasma cell infiltration, similar areas are also seen beneath the pelvic mucosa.

ORAL ADMINISTRATION OF CCl_4 TO ADULT DOGS

Repeated massive doses. Given a pure specimen of CCl_4, the pathologist would first want to know what lesions occur in dogs dying after receiving repeated large oral doses of the drug. Accordingly, to three animals 25 cc. CCl_4/kgm. of body-weight was given by stomach tube and the dose repeated every day or every other day. These dogs, receiving 1225, 1270 and 2175 cc., respectively, died on the seventh, tenth and sixteenth days of the experiment respectively.

Gross visceral changes were not particularly striking but were uniform in this series. *Lungs* were rather wet and, especially over the posterior surfaces, there were small discrete hemorrhagic areas. *Intestinal* mucosae were rather thin in places, but no frank ulcerations or definite bleeding points could be found. There were no worms. *Kidneys* appeared to be normal. *Livers* were pale yellow in color but practically normal in consistency. Red liver tissue could be seen as pin-head areas only about the portal radicles, while the rest of the lobule was of an opaque yellow appearance. These yellow areas appeared as connecting bands running from one lobule to another and gave rise to a trabeculated appearance which we shall speak of as a *tracery*. It was

equally conspicuous on exposed and cut surfaces. *Jaundiced* tissues were noted only in the seven-day dog.

Microscopically, *the outstanding and significant lesion is a change in the central part* of the liver lobules (see fig. 1). Parenportal radicles. Even these cells contain fat droplets, especially those more centrally situated. Capillaries and Kupffer cells are everywhere intact. However, many of the latter in the centers of lobules are filled with brown (iron) pigment. *Kidney* lesions are

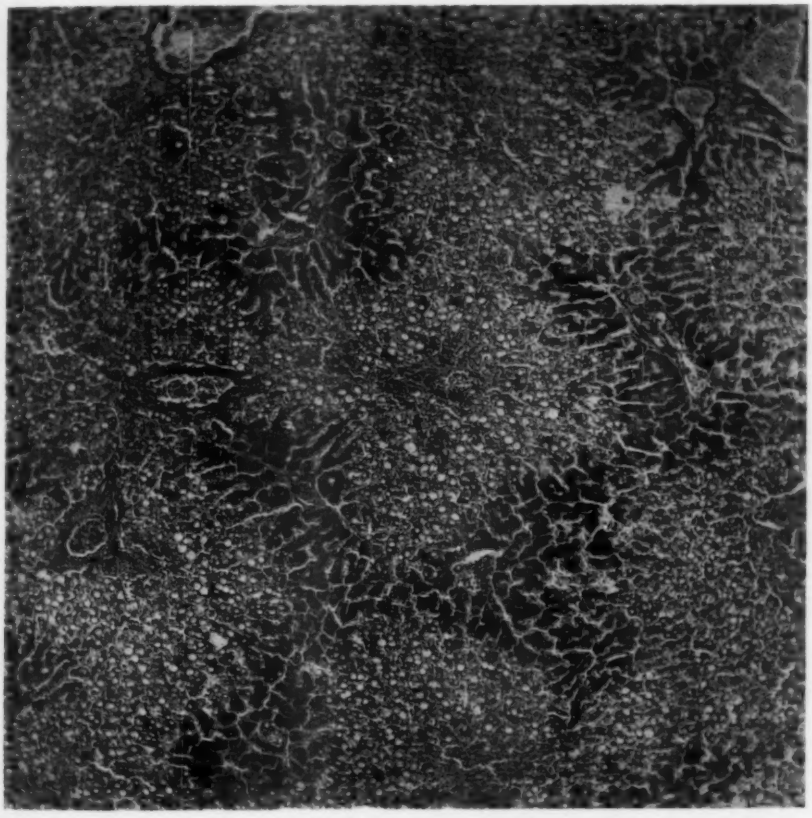

FIG. 1. DOG 31, GIVEN 25 CC. CCl_4 KGM. DAILY—TOTAL 1225 CC., DIED ON SEVENTH DAY

Section of liver, × 100, H. & E., shows periportal liver cells quite intact and parenchymal cells about the hepatic veins either absent or replaced by fat droplets. Necrotic tissue has all been removed.

chymal cells about the hepatic veins have disappeared except for a few which are completely filled with fat. No dead tissue is seen in the central zones, while in the peripheral portions of the lobules less damaged liver cells remain as small islands about the

not striking. Around some of the glomerular tufts within Bowman's capsule there is an accumulation of granular, eosin-staining material (albumin) (see fig. 2). There is also moderate cloudy swelling of convoluted tubular epithelium but no fatty change or

necrosis of these cells is found. In *lungs*, the red patches are found to be localized areas of hemorrhage and brassy-appearing edema. Bronchi and alveoli are filled equally, but no points of capillary rupture can be found. Many red blood cells in these areas are laked. No thrombi are seen in the pulmonary vessels. *Small intestines* show loss of tissue, but no frank ulcers are found, nor is anything noted which could explain the blood observed in the stools clinically. *Adrenals* do not show necroses. Sections from other organs show no lesions.

Single smaller doses. Attention was next directed toward a determination of the smallest dose following which histological indications of damage become apparent. Lamson and McLean (8) had found that 4 cc./kgm. was the minimum dose with which they could obtain an indication of

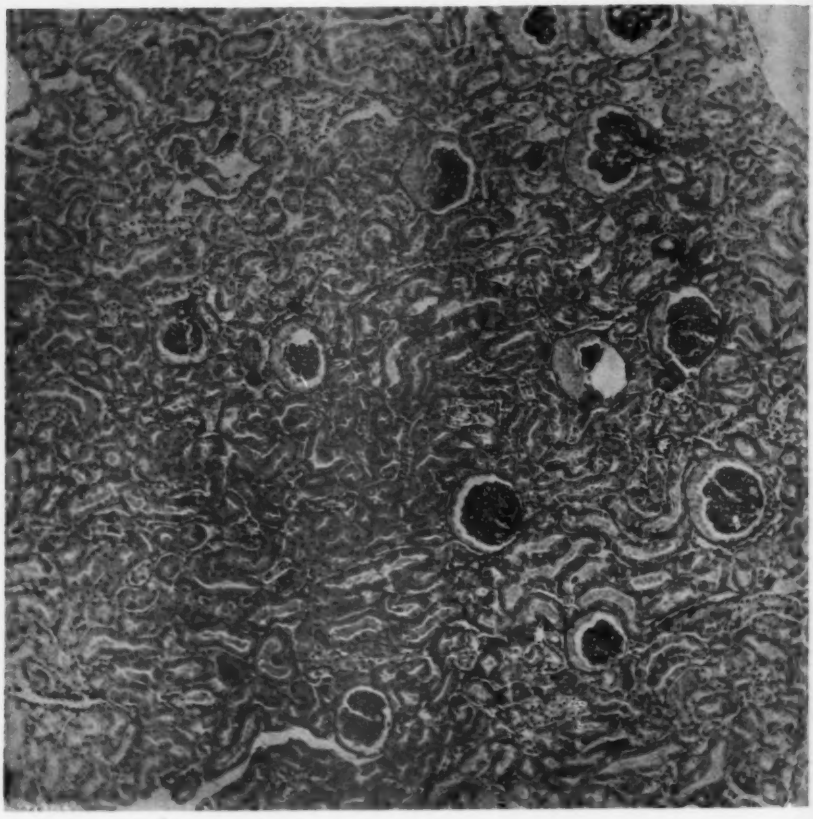

FIG. 2. KIDNEY SECTION FROM SAME ANIMAL AS FIG. 1

× 100, H. & E. Albuminous fluid is found about almost every glomerulus. There is also some cloudy swelling of convoluted tubular epithelium.

damage with the phenoltetrachlorphthalein test for liver function. However, it was known (4) (6) that histological liver changes occur with much smaller doses. Furthermore, we wanted to determine the possibility of quantitating liver damage histologically following the ingestion of CCl_4, since Meyer and Pessoa (6) had reported that "dogs which received the largest dose show the most marked lesions."

A large series of dogs was given varying size doses of CCl_4/kgm. of body-weight as follows: 0.01, 0.05, 0.1, 0.25, 0.5, 1, 2, 4, 6, 10, and 20 cc. Other studies described below (see p. 115) had shown that the most marked liver changes occur about forty-eight hours after CCl_4 has been given. Consequently, it was after such an interval that most of these dogs were killed. Only 1 dog received 20 cc./kgm., but at least 2 received each of the other amounts, and in one instance the series for a given dose includes 26 animals.

1. *0.01 cc./kgm.* In 2 dogs killed forty-eight hours after receiving this dose, worms were found. One was infested by both roundworms and hookworms, the other by roundworms only. No other abnormalities were encountered either in the gross or microscopically, except those which are constantly found in canine tissue.

2. *0.05 cc./kgm.* Although there is no unanimity of practice in administering CCl_4 therapeutically, yet from communications by Hall (9), Lambert (5), and Smillie and Pessoa (10), it was gathered that the average effective dose for man is about 3 cc. For an average adult this is equivalent to 0.05 cc./kgm. of body-weight. Deaths have occurred among children subsequent to the ingestion of a similar amount (3) (11).

Eight dogs were given 0.05 cc. CCl_4/kgm. and observed from two days to two weeks. At no time did any of them show signs or symptoms which could be interpreted as deleterious effects following ingestion of CCl_4. Two of these dogs were killed after a lapse of forty-eight hours, 2 after five days, 2 after seven days and 2 after fourteen days, following administration of the drug. At autopsy no hookworms were found; 2, however, were infested by tapeworms.

The microscopical findings are not uniform, striking or significant. Most *liver* sections are normal, some show hydropic change in the parenchymal cells (see p. 131), while others present a slight degree of paleness and swelling of the pericentral cells, similar to that found in controls. In some sections of *kidney* there are long cortical zones of cellular infiltration—as in an old pyelonephritis; the cortical tubules in others are lined in places by cells filled with fat. These renal changes are encountered so frequently in canine tissue that they are held to be of no significance here. Sections from other organs show nothing which would lead even to suspicion of damage from the administration of CCl_4.

3. *0.1 cc./kgm.* Two dogs receiving this amount of CCl_4, were killed forty-eight hours later. At autopsy no worms were found and no lesions observed on gross examination of the viscera. Microscopically, *liver* cells about hepatic veins are slightly swollen and stain less intensely. There is no necrosis and other organs show no pathological changes.

4. *0.25 cc./kgm.* Two dogs received this dose and were killed after forty-eight hours. At autopsy no worms were found and no gross lesions noted in any organ. Tissue for microscopic study was taken only from kidneys and liver.

Sections of *kidney* show a few cortical areas of cellular infiltration, while in the *liver* there is swelling and paleness of parenchymal cells about hepatic veins. The swollen cells contain many finely divided fat droplets but there is no necrosis.

5. *0.5 cc./kgm.* Two dogs were given this amount, and forty-eight hours later were killed. In the gross, no worms were found, but there was a perfectly distinct translucent trabecular tracery outlining the liver lobules. Tissue was saved only from kidneys and liver.

Microscopically, the *liver* presents a frank fresh central necrosis. In necrotic areas liver cells are swollen, fragmented and stain quite palely in marked contrast to intact cells about portal radicles. There are many fat droplets in the dead and damaged cells, and their nuclei show various degrees of degeneration. Zones of necrosis run continuously from one lobule to another and account for the trabecular tracery noted in the gross. As yet no phagocytosis of dead tissue is apparent; Kupffer cells and capillaries are uninjured. Even intact parenchymal cells about the portal veins have been damaged, as they are swollen and their cytoplasm is granular. *Kidneys* show no pathological changes.

6. *1 cc./kgm.* Two dogs were killed forty-eight hours after receiving this dose. At autopsy no worms were found. The *liver* of each presented trabecular tracery. Kidneys from one showed many narrow, golden-yellow lines of fatty tissue in the cortex, extending upward from the pyramids, not quite as far as the capsule.

Microscopically, there is central necrosis of the liver, quite like and apparently no more extensive than that which followed the ingestion of 0.5 cc./kgm. *Kidneys* from both dogs show cortical areas of cellular infiltration and many of the cortical tubules are lined by cells full of fat. As has been stated, we attach no significance to such renal findings.

7. *2 cc./kgm.* Two dogs received this dose and were killed forty-eight hours later. At autopsy no worms were found; the liver of each showed translucent trabecular tracery.

Microscopically these *livers* show extensive fresh central necrosis in which fully half the parenchymal tissue is involved. It remains *in situ* as a coagulated pink-staining mass of cellular debris, interspersed between intact capillaries. Liver cells about portal radicles appear as small islands of normal tissue. Separating these two zones there is a narrow band of live but damaged liver cells heavily laden with fat droplets. Sections from other organs reveal no lesions worthy of mention.

8. *4 cc./kgm.* More dogs received this than any other dose since it was the most convenient one with which phenoltetrachlorphthalein curves and blood chemistry analyses could be made. This series of dogs is considered later (p. 114) in an effort to trace liver lesions from the earliest recognizable evidence of damage through the various stages of development, healing and repair.

One of 5 dogs receiving 4 cc./kgm. died after forty-eight hours, the others were killed after the same time. Two, because of vomiting, were unsatisfactory. *Livers* of the other three showed trabecular tracery and, microscopically, extensive fresh central necrosis. In *kidneys* of several, cortical tubules are lined by cells filled with fat droplets; in one, small accumulations of pink, granular, albuminous substance are found within Bowman's capsule. Thorough study of all other organs reveals no further lesions.

9. *6 cc./kgm.* Six dogs received this dose and were killed from *one to two weeks* later. At autopsy, from

pale narrow bands of tracery throughout the *livers* it was evident that central necrosis had been present.

Microscopic sections support the interpretation of gross findings, although the time interval since dosing had been sufficient to permit removal of necrotic cells. Only collapsed framework of capillaries and Kupffer cells remains in the central zone where necrosis has occurred. Other organs show no lesions worthy of mention, except that in the *adrenals* of a dog sacrificed after eleven days, there are a few small foci of necrosis in the cortex.

10. *10 cc./kgm.* Two dogs received this dose; one became very sick and died within forty-eight hours; the other was killed after five days.

The dog which died showed in the gross a pale, swollen *liver*, normal appearing red liver tissue being present as pin-head depressions between raised bands of translucent tracery. Microscopically, there is an exquisite early central necrosis (see Fig. 3); 75 per cent of parenchymal tissue has been destroyed. It all remains *in situ*, however, as a pale, pink-staining mass of cellular debris. There is moderate cloudy swelling

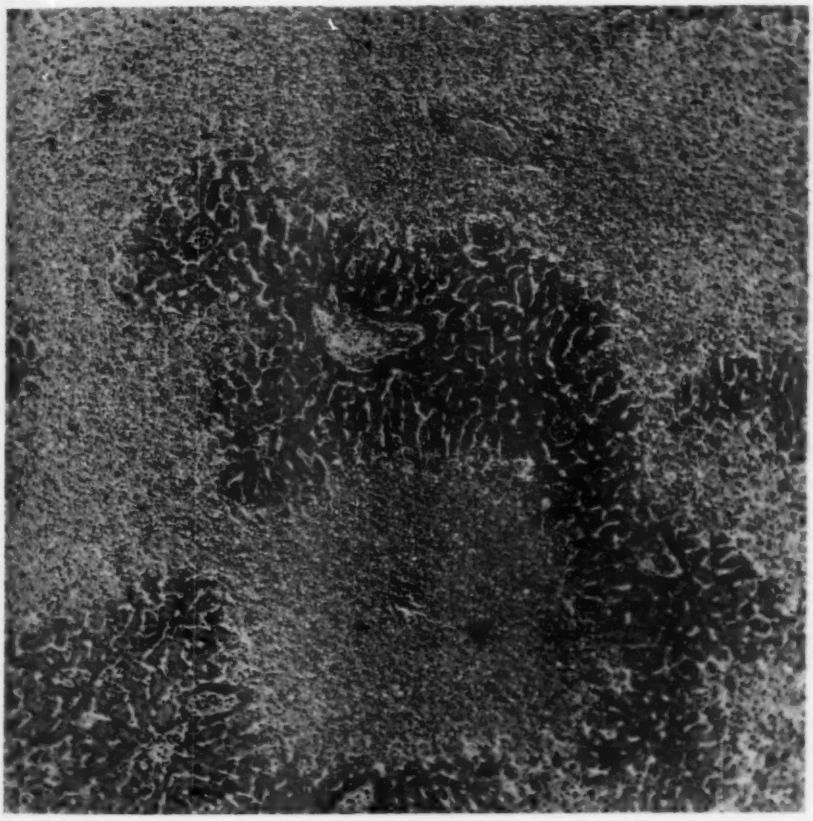

FIG. 3. DOG 50

Liver H. & E., × 100, shows the extensive central necrosis in an animal which died forty-eight hours after receiving 10 cc. CCl_4/kgm.

of *renal*, convoluted tubular epithelium; but other organs show no lesions.

The dog killed after five days was pregnant. Grossly, there was no liver tracery. Microscopically, liver parenchymal cells are hydropic and there is an inconspicuous regressing central necrosis—not all lobules are involved. From clinical behavior (1, p. 239, Fig. 7, G-12) and histological findings we feel justified in assuming that this dog did not retain all the CCl_4 administered.

11. *20 cc./kgm.* One dog receiving this dose was killed after *four and one-half hours*. In the gross the liver appeared to be somewhat swollen and pale; there was mild hyperemia of *gastric* and *intestinal* mucosae. Microscopically, in the *liver* there is paleness and cloudy swelling of central parenchymal cells, most of which contain finely divided fat droplets. However, there is no hepatic necrosis and other organs show nothing abnormal.

DEVELOPMENT AND RECESSION OF LIVER LESIONS FOLLOWING ORAL ADMINISTRATION OF 4 CC. CCl_4 PER KILOGRAM

Most phenoltetrachlorphthalein liver function tests and blood chemistry analyses reported in our previous communication (1) were carried out on dogs which had received 4 cc. CCl_4 /kgm.; consequently an abundance of material was at hand from this particular dose. It was considered advantageous to kill these dogs after varying intervals in order to observe in detail the development, recession, and healing of the liver lesions. Such study is of value to determine, in cases of death following ingestion of CCl_4, whether the lesions encountered are comparable to those produced experimentally, after a similar time interval, in dogs given CCl_4.

Twenty-six dogs, each receiving 4 cc./kgm. were used in these experiments. One died after forty-eight hours, the others were killed from six hours to five weeks after dosing.

1. *Six hours.* In 2 dogs killed after this interval, no worms were found and no gross lesions noted. However, in the intestinal contents there was a pronounced odor of CCl_4. Microscopically, the only departure from normal is in the *liver*, where pericentral parenchymal cells stain less intensely and are swollen. It is so marked here that we consider this change pathological.

2. *Twelve hours.* Two dogs killed after twelve hours showed in the gross an indefinite, pale, gray, trabecular liver tracery. No worms were found in the intestines.

Microscopical examination of tissue from all organs, save the *liver*, is negative. There is cloudy swelling and paleness of the liver cells about the hepatic veins. Parenchymal cells about portal radicles stain normally. The two portions of the lobule are separated by a narrow midzonal band of liver cells filled with fat droplets. Fully one-half the total liver tissue is involved in this central swelling. A few parenchymal cells, nearest the hepatic vein, are dead; cell outlines are indistinct and nuclear material is fragmented and pycnotic.

3. *Twenty-four hours.* In 2 dogs, killed one day after dosing, fairly definite liver tracery was noted. The colonic contents of 1 animal gave off the pungent odor of CCl_4, and in the lungs there were numerous firm, dark red, discrete, hemorrhagic patches.

Microscopically, these *lung* changes are focal hemorrhages surrounded by

accumulations of brassy edema. The *liver* of one shows a well marked central necrosis with about one-third the total tissue dead. In the other there is no actual necrosis, but only paleness and swelling of central cells, many of which are loaded with finely divided fat droplets. It is interesting that the liver of one dog, after a day, shows definite necrosis while that of the other shows a lesion no farther developed than after twelve hours.

4. *Forty-eight hours.* One dog died two days after receiving CCl_4; 4 others were killed after this interval. As 2 of the latter are unsatisfactory because of vomiting, they will not be considered further. In the gross, all animals showed a gray, translucent tracery extending over the entire liver surface. In the lungs of the dog that died, there were numerous discrete hemorrhagic areas.

Microscopically the *pulmonary* changes are focal hemorrhages surrounded by areas of brassy edema into which leucocytes have infiltrated. In the *livers* there is a beautiful central necrosis. Fully one-half the liver tissue is dead. Necrotic cells stain faintly, are fragmented and their nuclei are degenerating. However, capillaries in necrotic zones are intact and Kupffer cells are undamaged. Live, intact, periportal liver cells are sharply demarcated from the central zones of necrosis, not only by differences in intensity of staining but also by a mid-zonal band of fat-containing liver cells. These latter have been damaged, no doubt, but are not dead, since their cell membranes and nuclei are intact even though their cytoplasm is largely replaced by fat. In the *kidneys* of the dog which died there is a mild cloudy swelling of convoluted tubular epithelium and an escape of albuminous material into Bowman's capsule. Other dogs show some fat in lining cells of a few cortical tubules. Sections from other organs reveal no lesions.

5. *Four days.* Two dogs were killed after this interval. At autopsy they were found to have pale livers in which definite but not extensive trabecular tracery was seen. There were vertical streaks of golden-yellow fat in the renal cortex.

In sections there is evidence of a recent well-marked *central necrosis* (see Fig. 4); however, dead cells from these zones have been almost entirely removed. A collapsed framework of capillaries with intact Kupffer cells remains about the central veins. Liver cells adjacent to these collapsed areas contain many large fat droplets, while periportal cells appear normal. Besides fat in tubular epithelium, one dog's kidneys are loaded with brassy tubular casts; however, there is no evident necrosis of tubular epithelium nor are there glomerular changes.

6. *Five days.* Two dogs killed after five days presented gross and microscopic changes quite like those after four days with the exception that neither had casts in the renal tubules.

7. *Seven days.* Three dogs were killed one week after receiving the drug. At autopsy only 1 showed liver tracery; this dog was pregnant. Another had a purulent sinusitis accompanied by bronchitis and patchy lobular pneumonia.

Besides gross complications, which microscopic sections verify, the only lesion is in the *liver*. There is healing central necrosis. All dead tissue from

central zones has been removed, leaving behind a collapsed framework of intact capillaries and undamaged Kupffer cells. Some of the latter are full of brown pigment (iron). Many infiltration, as specific stains are negative.

8. *Two weeks.* Three dogs were killed after this interval. No gross lesions were found at autopsy.

FIG. 4. DOG 76, GIVEN 4 CC. CCl_4/KGM.—KILLED AFTER FOUR DAYS

Section of liver, H. & E., × 100, shows the necrotic material almost entirely removed; wide scar-like zones of collapsed capillaries have replaced the picture of necrosis. Capillaries are intact—no regeneration is seen.

intact, apparently undamaged, periportal liver cells are hydropic (see Fig. 5), that is, the cells are swollen, stain palely and the cytoplasm is reticulated. This is not the result of fat

Microscopically, in 1 dog, the epithelial cells of the convoluted tubules and loops of Henle contain fat. Lesions common to all are found in the *liver*. There is healing central necro-

sis as shown by areas of collapsed intact capillaries about the hepatic veins. Kupffer cells in these zones are laden with brown (iron-containing) pigment, and adjacent liver cells contain fat droplets. Periportal liver cells are normal. No histological evidence of regeneration is detected, at least no young budding liver cells are seen. However, regeneration must be going on, since grossly the livers were of normal size and, microscopically, individual liver lobules are not conspicuously narrowed. Sections from other organs show nothing remarkable.

9. *Three weeks.* Three dogs were killed after this interval. At autopsy they presented no significant lesions. One had *strongyli* in the chambers of the right heart and much fat in the renal cortex; another was infested by roundworms.

Microscopically the *livers* of all show healing central necrosis with stellate areas of collapsed tissue about hepatic veins and brown, pigment-bearing Kupffer cells in these zones. No proliferating young liver cells are seen. In 1 dog (a very fat dachshund) there is a wide mid-zonal band of liver cells, surrounding the collapsed areas, filled full of fat droplets. The same dog has a great deal of fat in lining cells of many cortical tubules. No lesions of significance are found in sections from other organs.

10. *Four and five weeks.* The last 2 dogs were killed, one after each of these intervals. At autopsy no pertinent lesions were discovered, although one had a purulent sinusitis, bronchitis and lobular pneumonia.

Microscopically, there are stellate areas of intact capillaries about the hepatic veins. Pushing into these areas, between capillaries, one can see a few young liver cells. In one there is an adjacent zone of liver cells filled with fat droplets and in the other a diffuse hydropic change of all parenchymal cells.

Effect of low temperature. We thought it appropriate here to compare two other series with dogs receiving 4 cc. CCl_4/kgm. The first consists of two dogs given 4 cc. CCl_4/kgm., but kept in an ice chest at 12°C. for a day before and a day after dosing (1, p. 277). They were killed after one and two and one-half weeks, respectively. Neither in the gross or on microscopical examination of the tissues is it possible to discern any significant differences between these dogs and those kept at room temperature.

6 cc. CCl_4/kgm. Six dogs received this dose and form the second series. They were killed in pairs, eight days, eleven days and two weeks after administration. In the gross they all presented an indistinct liver tracery. Microscopically, in each there is healing central necrosis quite like that found after a similar time interval when 4 cc./kgm. had been given. However, since these 6 dogs received 50 per cent more drug per kilogram than did those in the two preceding series, a greater destruction of liver tissue might have been expected. No increase was found and we doubt if the liver sections from these three series could be distinguished one from another.

EFFECT OF ADDING 4 CC. ALCOHOL TO THE CCl_4

Our attention was next directed toward a determination of effects following administration of alcohol with CCl_4. This is of practical importance. Lambert (5), Smillie and Pessoa (10), and Pessoa and Meyer (4), as well as others, have reported that chronic alcoholics and patients just over a "spree," are more ill following CCl_4 treatment than average individuals, frequently presenting clinical evidence of liver damage.

Ninety-seven per cent alcohol, administered by stomach tube and washed down with water, was used for these experiments. CCl_4 and alcohol are freely soluble in each other. Practically all dogs became intoxicated soon after receiving the alcohol-CCl_4 mixture.

1. *Controls.* Thirteen dogs received 4 cc. 97 per cent alcohol/kgm. diluted with water. Two were killed after four days; 6 after one week; and 5 after two weeks. Two are excluded from further consideration because of obvious laboratory errors. At autopsy nothing of import was found

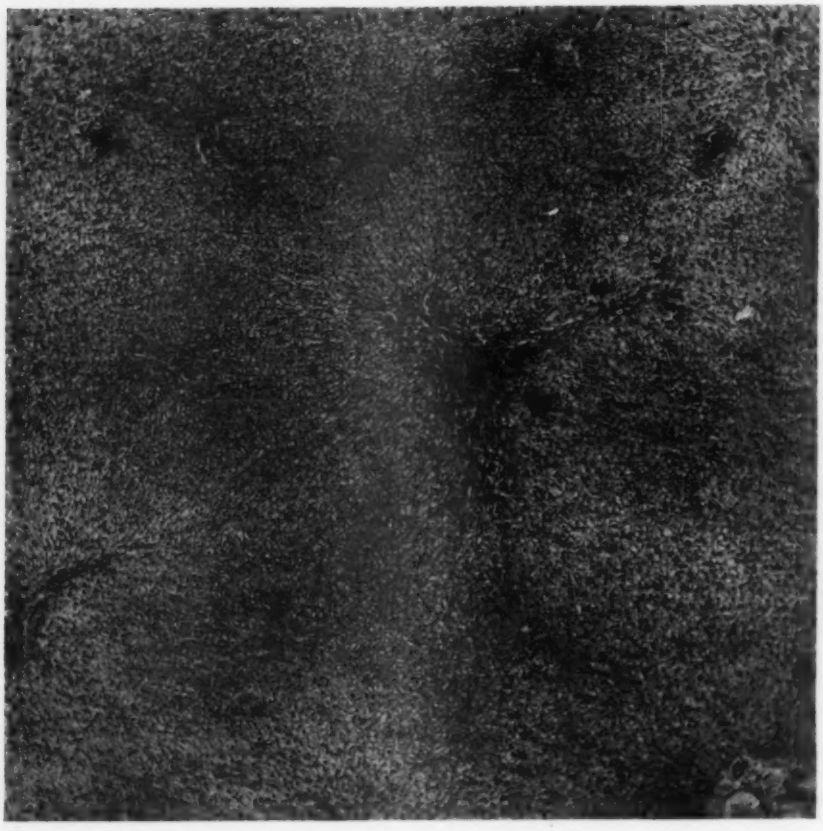

FIG. 5. DOG 147, GIVEN 20 CC./KGM. OF WARMED CREAM FOLLOWED BY 4 CC. CCl_4/KGM.—KILLED AFTER THREE WEEKS

Section of liver, H. & E., × 100, shows the stellate areas of collapsed capillaries, evidence of a previous central necrosis. The liver cells are all *hydropic*, swollen, clear, apparently entirely vacuolated. This appearance is not due entirely either to fat or glycogen.

either in the gross or microscopically. There is an abundance of literature confirming this observation that *single large doses of alcohol do not produce demonstrable liver changes.*

2. *4 cc. alcohol with 0.05 cc. CCl_4.* Ten dogs received a human therapeutic dose of CCl_4 (0.05 cc./kgm.) with 4 cc. alcohol/kgm. Some vomited; all were killed after forty-eight hours. Not one, including those which retained all the dose, shows liver damage which can be attributed to CCl_4; a few present focal abscesses and hydropic changes in parenchymal cells, but there is no central lesion.

3. *4 cc. alcohol with 0.1 cc. CCl_4/kgm.* Four dogs received 0.1 cc. CCl_4/kgm. with 4 cc. alcohol/kgm.; they were killed forty-eight hours later. Microscopically the *liver* of each shows swelling and paleness of parenchymal cells about the central (hepatic) vein. There is well-marked infiltration of fat droplets into these cells. No definite necroses are seen but it is conspicuous that liver damage is more extensive than in dogs receiving a similar dose of CCl_4 without alcohol.

4. *4 cc. alcohol with 4 cc. CCl_4/kgm.* Nine dogs were given 4 cc. each of alcohol and CCl_4/kgm. Two died in twenty-four hours, 2 in forty-eight hours, 1 was killed after three days, 1 after two weeks, 2 after three weeks and the last, four weeks after dosing.

Dogs which died in *twenty-four hours* showed, in the gross, striking translucent trabecular liver tracery as well as bloody mucus in the upper intestinal tract. The colon and caecum of one were plugged by masses of whip and roundworms. Tissues of the other were jaundiced. The increase in serum bilirubin in these animals has been discussed in our previous paper (1). Microscopically, the origin of the bloody mucus is not found. In the *liver* there is tremendous early central necrosis (see Fig. 6); fully 90 per cent of the parenchyma is necrotic, only a narrow rim of live liver cells remains about each portal radicle. There is mild cloudy swelling of renal convoluted tubular epithelium, but sections from other organs reveal no further damage.

Two dogs dying in *forty-eight hours* showed, at autopsy, a few small hemorrhagic patches in the lungs, especially over the posterior surfaces. No jaundice was noted but the pale yellow livers presented considerable translucent tracery. Upon microscopical examination a few large phagocytes filled with cellular debris are found in the pulp of both spleen and mesenteric lymph glands. Presence of fresh *pulmonary* hemorrhages is confirmed and the livers are severely damaged. Here again there is an extensive central necrosis with dead tissue sharply demarcated from live *liver* cells about portal radicles. Many convoluted tubules and loops of Henle are lined with fat-laden cells, there is some cloudy swelling of cortical parenchyma, and within Bowman's capsule there are accumulations of pink-staining albuminous material. Sections from other organs show nothing worthy of note.

The dog killed *three days* after dosing showed, at autopsy, extensive translucent *liver* tracery. Microscopically, about 60 per cent of the liver tissue is dead, the central zone is affected while periportal cells remain unaltered. However, there is some collapse of tissue in central zones with beginning phagocytosis.

In the dog killed *two weeks* after dosing, 2 after *three weeks*, and the last 1 after *four weeks*, lesions of importance are found only in the liver. They are microscopic and consist of collapse of capillary framework about hepatic veins; brown, pigment-bearing Kupffer cells are seen in these areas and growing into the collapsed zones an occasional young liver cell can be found. In two dogs there is hydropic change in all liver cells except young budding ones.

a. 1 cc. alcohol/kgm. with 4 cc. CCl_4/kgm. In an effort to determine the effect of varying the amount of alcohol given with a constant amount of CCl_4,

seven dogs received 1 cc. alcohol/kgm. with 4 cc. CCl_4/kgm. They were autopsied from forty-eight hours to four weeks after dosing.

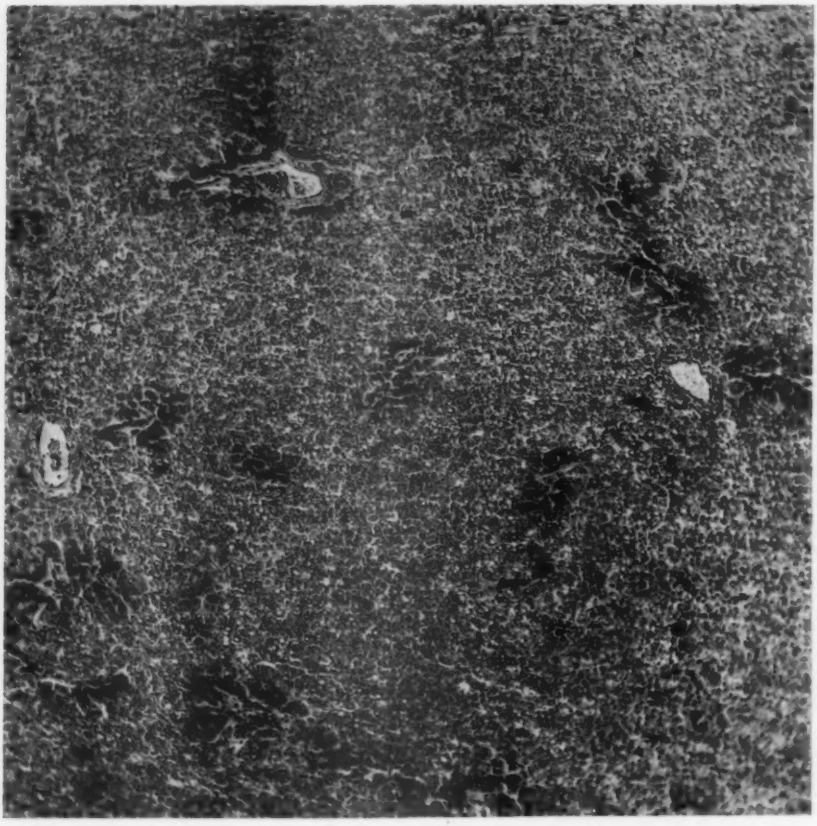

FIG. 6. DOG 83, GIVEN 4 CC./KGM. EACH OF CCl_4 AND C_2H_5OH, DIED IN FORTY-EIGHT HOURS

Section of liver, H. & E., × 100, shows extreme central necrosis with only a narrow rim of live liver cells remaining about the portal radicles. The picture is similar to that found in puppies given CCl_4 without alcohol.

The first two autopsied died during the *second day* of the experiment. One showed gross autolytic changes; tissues of the other were jaundiced. *Livers* presented well marked translucent tracery. Microscopically, from 75 to 90 per cent of the liver tissue is dead; the lesion is an extensive central necrosis. Sections from other organs do not differ materially from those in the dogs autopsied forty-eight hours after receiving 4 cc. CCl_4/kgm. without alcohol. It is quite apparent that liver damage is more extensive when alco-

hol is added to this dose of CCl_4; furthermore, the death rate is higher. However, increasing the amount of alcohol administered does not affect materially the apparent degree of liver damage, although the death rate is doubled.

In the dog killed *one week* after dosing, microscopically there are accumulations of pink-staining albuminous material within Bowman's capsule and also a healing central necrosis of the liver with collapse of framework, absence of dead cells, and no damage to periportal cells.

The dog killed after *two weeks* shows microscopically healing central *hepatic* necrosis with a fringe of fat-laden parenchymal cells bordering the collapsed areas. In the *kidneys*, besides cortical tubular lining cells full of fat, there is chronic nephritis with scarring, distortion and dilatation of tubules, in some of which are hyaline casts.

The last three dogs killed after *three* and *four weeks*, show microscopically healing central necrosis of the liver, with stellate areas of collapsed framework, consisting of intact capillaries and Kupffer cells laden with brown pigment. Into some of these areas young liver cells can be seen sprouting from adjacent parenchymal cells. It would be difficult to distinguish these liver lesions from those occurring in straight 4 cc.CCl_4/kgm.

5. *4 cc. alcohol with 10 cc. CCl_4/kgm.* Five dogs were given this dose; 1 died in sixty hours; 2 were killed after five days and the others two weeks after dosing.

At autopsy, organs from the dog which died were autolysed and tissues were jaundiced. There was marked translucent trabecular liver tracery. Microscopically, fully 75 per cent of the *liver* parenchyma is involved in a central necrosis. However, there is little if any more destruction than followed the ingestion of 10 cc. CCl_4/kgm. without alcohol. In the *kidneys* there is cloudy swelling and accumulations of albuminous material are found within Bowman's capsule of some glomeruli.

Dogs killed *five days* after dosing showed in the gross indistinct liver tracery. One was pregnant and had streaks of lipoid in the kidney cortex. Microscopically, there is healing central necrosis of the liver such as was found five days after administering 4 cc. CCl_4/kgm.

Dogs killed after *two weeks* presented, in the gross, indefinite liver tracery and microscopically evidence of healing central necrosis with a few young cells growing into pericentral collapsed areas. One shows marked hydropic change in all parenchymal cells.

EFFECTS OF ADDING OILY SUBSTANCES TO CCl_4

1. *Cream.* Eight dogs were starved for forty-eight hours and then given, by stomach tube, 20 cc./kgm. of warmed cream. One hour later they each received 4 cc. CCl_4/kgm. One died in forty-eight hours, another was killed after five days, 2 after a week, 2 after two weeks and the last pair three weeks after dosing.

At autopsy, the liver of the animal which *died* was pale and showed tracery. The *kidneys* also were pale. Microscopically, 75 per cent of the *liver* parenchyma is dead, involved in the central necrosis. There is cloudy swelling of *renal* tubular epithelium and accumulations of albuminous material are found within some Bowman's capsules. These liver lesions are more marked than in the straight 4 cc. CCl_4/kgm. series, but are comparable to those found after the addition of alcohol.

The dog killed *five days* after dosing shows microscopic evidence of a receding central necrosis of the *liver*. Not all debris has been removed from the central zones of collapsed framework. Adjacent liver cells contain fat droplets and periportal liver cells appear undamaged. *It is interesting that this dog, despite histological evidence of severe liver damage, had no marked alteration in the phenoltetrachlorphthalein curve.*

Dogs after *one week* show stellate areas of collapsed capillaries about the central veins. However, there is nothing to differentiate them from other dogs receiving 4 cc. CCl_4/kgm. one week previously.

Dogs killed after *two* and *three weeks* show microscopically that a central necrosis of the liver had been present, that it is healing and that regeneration of liver cells into collapsed pericentral areas is under way. There is hydropic change in most of the intact liver cells, (see Fig. 5).

2. *Olive oil.* Dogs which had received nothing to eat for forty-eight hours were given 4 cc./kgm. each of olive oil and CCl_4. They were not so sick as dogs receiving cream before the CCl_4. Not one of the 8 died. One was killed after four days; 2 after a week; 2 after two weeks and 2 more after three weeks. At autopsy and upon examining the microscopic specimens from these dogs, there are unmistakable signs of pre-existing central necrosis. It has progressed beyond the acute stage and is now in one or another of the stages of healing and repair. There is nothing found histologically which would indicate that olive oil affects the degree of liver destruction when given with CCl_4.

3. *Paraffin oil.* CCl_4 is freely soluble in paraffin (mineral or white) oil. The latter supposedly is not absorbed from the intestinal tract. As has been suggested by others, administration of paraffin oil with CCl_4, theoretically, is ideal since hookworms should be killed and less drug absorbed by the host. Two dogs received 0.25 cc. CCl_4/kgm. and were killed after forty-eight hours; two others received 0.5 cc. CCl_4/kgm. and were killed after the same interval, while eight receiving 4 cc. CCl_4/kgm. were killed after five days. The four receiving smaller doses of CCl_4 each were given 25 cc. of oil while the eight dosed with 4 cc. CCl_4/kgm. also received 4 cc./kgm. of paraffin oil.

On gross examination no hookworms were found (we do not know if these dogs were infested before being dosed), but animals receiving 0.25 cc. CCl_4/kgm with oil were infested by round and tapeworms. No visceral lesins were found.

Microscopically, the liver of 1 dog receiving *0.25 cc. CCl_4/kgm.*, is normal while the other one shows a generalized swelling and paleness of pericentral liver cells into which finely divided fat droplets have infiltrated. After receiving *0.5 cc. CCl_4/kgm.*, 1 dog shows a well marked central necrosis of the liver, bordered by a zone of fat-laden parenchymal cells. The other animal has no definite necrosis but does show swelling and a paleness of pericentral cells. In the kidney cortex there are areas of cellular infiltration, and fat is found in lining cells of many tubules. Of 8 dogs given *4 cc. CCl_4/kgm.* with paraffin oil and killed after five days, all but one show definite evidence of healing central necrosis. There are stellate areas of collapsed tissue about central veins and normally intervening liver cells are missing. In some sections adjacent liver cells are hydropic, in others normal, and in others they are heavily laden with fat droplets.

From data just enumerated it can be concluded that if administration of paraffin oil with CCl_4 has any effect on the degree of liver damage, it is slight. There is no evidence that damage is intensified and only the most meagre basis for concluding that

it is decreased. However, none of these dogs died.

INHALATION OF CCl_4 VAPOR

CCl_4 was used as early as 1865 as a general anesthetic. It was soon found, however, that chloroform produced more profound anesthesia and its use was attended by fewer dangers. Consequently, today CCl_4 as a practical anesthetic is unknown. Sporadic cases of poisoning appear from time to time, however, as the result of inhalation of CCl_4 vapor in commercial pursuits (12) (13).

The apparatus in which our dogs were allowed to inhale CCl_4 vapor and the several stages through which they pass in reaching complete anesthesia have been described (1, p. 229). We were desirous of knowing whether the inhalation of CCl_4 is effective as a vermifuge; also the severity of the kidney lesions.

Many dogs used for inhalation experiments were not autopsied. However, 2 were killed with concentrated vapor, eight and eleven minutes, respectively, following immersion. Another one was kept at Stage III (just preceding loss of coördination) for one hour and killed ten days later. Three were kept at Stage V (complete relaxation) one hour; 1 died after forty-eight hours, another was killed after the same interval and the third died after six days. Two dogs were kept at Stage V for an hour on each of five successive days; the first was killed on the fifth day of the experiment and the other on the seventh day. Another was given 123 exposures to concentrated vapor in a bell-jar, totalling three and one-quarter hours and extending over a month. This dog died six weeks after the experiment was started.

Two dogs, *killed quickly with concentrated vapor*, showed intestinal worms, no hookworms, however. Fresh hemorrhages were found all through the liver of one dog, chiefly beneath the capsule. Otherwise, autopsies were negative. It is our impression that these hemorrhages were traumatic in origin, the result of too vigorous efforts at resuscitation.

The dog killed ten days after being kept at *Stage III for one hour*, shows a mild healing central liver necrosis, definite but not extensive. There is also lobular pneumonia with ulcerative bronchitis.

Three dogs kept at *Stage V for one hour* show central necrosis of the liver, fresher, of course, in the forty-eight hour than the six-day animal. In dogs which died there are accumulations of albuminous material about many glomerular tufts.

Two dogs kept at *Stage V for one hour on each of five successive days*, had intestinal worms, hookworms in 1 case and tapeworms in the other. Both showed translucent trabecular liver tracery. Microscopically, in one there is an organizing pneumonia about the smaller bronchi. Both have a well marked fresh necrosis of the cells about the central vein, superimposed on a healing lesion. Adjacent liver cells are filled with fat droplets. Normal liver cells remain only about the portal radicles. No lesions are found in kidneys.

The dog *immersed repeatedly in concentrated vapor over a period of a month*, showed at autopsy tracery throughout the pale yellow liver and a great deal of fat in kidney cortex. Microscopi-

cally, there is mild bronchitis without any pneumonia; fat is found in lining cells of many cortical tubules; the liver lesion is one of healing central necrosis with stellate areas of collapsed framework about hepatic veins; adjacent liver cells in a wide band contain fat droplets.

INTRAVASCULAR INJECTIONS OF CCl_4

Injections into peripheral veins. Owing to the poor solubility of CCl_4 in water (1:1250) and since a stable emulsion could not be made by methods tried, the drug was injected in pure form into a convenient peripheral vein. As previously reported (1, p. 255), actions of dogs after intravenous administrations are most interesting and quite uniform. Usually, 0.154 cc. CCl_4/kgm. intravenously is lethal. This, however, is not always the case and sometimes dogs survive repeated injections of such an amount.

There are 21 animals in this series of peripheral vein injections; most of them died within a few hours; some, after surviving the initial dose for four days, were killed by larger or oft-repeated smaller doses. Three were allowed to live one week and were then killed so that late pathological changes might be studied.

Gross findings at autopsy were striking and uniform, among the *dogs which died.* In each there were lung changes; characteristically one found widely distributed, firm, red, non-air-containing patches, varying in size from 1 cm. in diameter to total involvement of a lobe. The *lungs* were heavy and wet; a great deal of pink, frothy fluid exuded from the bronchi as the lungs were removed, and from cut surfaces as the organs were sectioned. These patches were found most frequently along the free margins and in the dependent portions of the lungs. In several instances, free, bloody fluid was found in pleural cavities. Parasites, including hookworms, were found in the intestines of many. Other organs showed no lesions. In the lungs of 3 dogs killed *one week after injection,* only an occasional small, discrete, firm, red patch could be found. The minuteness and paucity of lesions was in marked contrast to conditions described as occurring a few hours after injection. Two of these 3 dogs had hookworms in their intestines.

Microscopic findings bear out gross observations. The striking lesion is in the *lungs,* where the red patches are found to be accumulations of fresh hemorrhage and brassy edema, together filling alveoli and bronchi over extensive areas. Laking and fragmentation of red blood cells in these edematous areas is striking—the source, no doubt, of the brassy color in the edema. There are no thromboses but occasionally the central part of these edematous areas is necrotic. Evidently, the process is one of infarction. In some dogs, allowed to live several days, there is lobular pneumonia. *The livers are strikingly free from zonal lesions;* in a few there is diffuse hydropic change in parenchymal cells. In some kidneys there are engorged glomeruli and in others accumulations of albuminous material about glomerular tufts. Sections of brain, in one case, from motor cortex, basal ganglia and dentate nuclei, show no lesions; sections from other organs are essentially normal.

Despite clinical findings to the con-

trary (1, p. 257), we have found no demonstrable liver damage following peripheral vein injections. The deleterious effects of CCl_4 administered in this way seem to be confined entirely to lung changes.

Intra-portal injections of CCl_4. Dogs given CCl_4 directly into the portal vein showed none of the striking blood pressure, respiratory or peculiar nervous phenomena, exhibited by those which received the drug in a peripheral vein (1, p. 259). Similar observations had been made previously by Chopra and McVail (14). Ten animals were given 0.154 cc. CCl_4/kgm. directly into the portal vein. Such a dose did not kill immediately as was so often the case after peripheral vein injections. However, most dogs were killed a few hours after intra-portal injections. Of 4 others injected under aseptic conditions, 1 was killed after twenty-four hours; another died after forty-eight hours; a third was killed after a week and the last one after three weeks. These latter 2 dogs were quite sick for four or five days following injection, refused food, were weak, became jaundiced and vomited a great deal. They then began to improve so that the three-week dog had been acting quite normally for a week, before being killed. Even as the clinical syndrome (1, p. 259) is quite different from that which has previously been reported for peripheral vein injections (1, p. 255), so are the pathological changes. In the former series the lungs bore the brunt of the attack and the liver went free; here the liver is profoundly damaged and lungs unaffected.

Gross liver changes in the dogs killed after a *few hours* are striking; over the dependent surfaces there are large greenish-brown areas of discolored, necrotic liver tissue, like infarcts. These areas varied in size from a few centimeters in diameter to involvement of an entire lobe. Centers of the individual areas of discoloration were yellow; this gradually merged into a green and more peripherally into a dirty brown zone, while the whole area was flanked by hemorrhagic tissue. Dogs autopsied after *twenty-four* and *forty-eight hours* were jaundiced, there was free bloody fluid in the peritoneal cavity and fibrinous adhesions were found over the areas of liver necrosis. In the livers of animals sacrificed *one and three weeks* after injection, depressed, gray, atrophic scars covered by fibrous adhesions and a thickened capsule designated sites of previous hepatic necrosis. Other organs showed no lesions.

Microscopically, the *liver* lesion is a diffuse necrosis with hemorrhage. In these dead areas most red blood cells are laked. From the margins of larger areas tongues of necrotic tissue extend into living parenchyma. In these extensions the necrosis seems to be periportal in contrast to the main mass which is a diffuse involvement. In the dog allowed to live *three weeks* such necrotic areas have been replaced entirely by stellate scars and collapsed capillary framework into which young liver cells are growing. The striking feature of these areas is the large number of wandering phagocytic cells full of brown pigment. Kidneys of dogs killed during the *acute stage* show at times a little cloudy swelling of convoluted tubular epithelium and an infiltration of albuminous material about glomerular tufts. In the twenty-four-hour dog there are many brassy hyaline casts in the tubules of both cortex and medulla. The majority of kidney sections show no lesions at all. In the *adrenals* of the dog dying after *forty-eight hours* there are a few inconspicuous foci of necrosis in the cortex. Other organs present no lesions worthy of comment.

Arterial injections. Two dogs were each given 0.154 cc. CCl_4/kgm. into the carotid artery. They were killed about an hour later. Grossly only a pale red edematous condition of the

meninges was found. One was infested by live hookworms. Microscopically, there is an accumulation of pink, granular, albuminous material in the pia arachnoid. No necroses are seen in the *brain*. Parenchymal liver cells about hepatic veins are swollen, granular and stain faintly; besides this zonal disturbance there is some diffuse hydropic change.

SUBCUTANEOUS INJECTIONS OF CCl_4

Five cubic centimeters of CCl_4 was injected subcutaneously in a dog's groin. There was no evidence of discomfort. Twenty-four hours later there was a 10 cm. pendulous mass at the site of injection. This area of swelling was not tender, nor was it fluctuant. The dog was killed on the third day of the experiment. The area of swelling was like jelly, consisting principally of edematous tissue, although in its center there was a small cavity filled with pus. No cultures were taken. The edematous condition had extended through the abdominal walls so as to involve subperitoneal tissues. The liver was pale and showed tracery.

Microscopically, in the jelly-like tissue the fixed tissues are spread apart by an infiltrating, edematous material, but few leucocytes are seen except at the abscess site. MacCallum-Goodpasture stains are negative for bacteria. There is well marked central necrosis of the liver from which some, but not all, necrotic cells have been removed.

INTRAPERITONEAL INJECTIONS OF CCl_4

Three dogs were used for this experiment. The first received 60 cc. CCl_4 and was killed two hours later. The others were given 20 cc. CCl_4 intraperitoneally; 1 died about fifteen hours later and the other was killed twenty-four hours after injection. At autopsy there were 80 cc. of bloody fluid in the peritoneal cavity of the first dog; from this fluid 33 cc. of CCl_4 were recovered by decantation. No lesions were found either in the gross or microscopically.

In the peritoneal cavity of each of the other dogs there was approximately 200 cc. of bloody fluid, in which a faint odor of CCl_4 could be detected. In the *liver* of each there is a well-marked early central lesion; the dog which died shows swelling and paleness of liver cells about hepatic veins, but the twenty-four-hour animal presents definite central necrosis with fragmenting cells and degenerating nuclei. In the *intestines* of this dog live hookworms were found. Sections from other organs show nothing worthy of note.

RECTAL ADMINISTRATION OF CCl_4

Two dogs received, respectively, 6.5 and 10 cc. CCl_4/kgm. by rectum. They were killed sixteen days later. At autopsy no gross lesions of consequence were found. Microscopically there are stellate areas of collapsed tissue about the hepatic veins—evidence of healing central necrosis. There is also diffuse hydropic change of most parenchymal cells. The histological evidence of pre-existing liver necrosis confirms the clinical observation that CCl_4 is absorbed per rectum (1, p. 266).

ORAL ADMINISTRATION OF CCl_4 TO OTHER ANIMALS

Puppies. Twelve pups, representing several litters and ranging in age

from one to three months, on the same day were each given by stomach tube 4 cc. CCl_4/kgm. Six (50 per cent) died, as contrasted with a death rate of 5 per cent among adult dogs. Ten pups were autopsied within the first three days of the experiment, the other two after six days.

At autopsy 7 of the 10 showed pronounced translucent liver tracery. Three of the 6 which died had masses of dead roundworms in their small intestines; 3 also had lobular pneumonia.

Microscopically, 4 have a lobular pneumonia. Each of the first 10 autopsied shows a tremendous fresh central necrosis of the *liver* in which from 50 to 95 per cent of the parenchyma is involved. In 1 case all that remains of live liver cells is the narrowest possible fringe about portal radicles. Necrosis is recent; dead fragmented liver cells are still *in situ* and no reparative processes are in evidence. This is a much more uniform and extensive liver lesion than occurred in adult dogs. In *kidneys* of pups which died there is mild cloudy swelling of convoluted tubular epithelium, but no serious renal changes are found. Sections from other organs show no lesions worthy of comment.

Pups killed after *six days* show stellate pericentral areas of collapse, the only remnant of pre-existing necrosis. There is also hydropic change in many parenchymal liver cells.

Rabbits. Since they cannot vomit, less error from this factor, found to be so important in dogs, would be encountered following the oral administration of CCl_4 to rabbits. It is not a new observation (15) that they die after receiving rather small doses of CCl_4. Unlike dogs, however, they show no signs of excitement but loll around their cages in a stuporous condition.

Twenty-six rabbits were given doses ranging from 0.1 to 15 cc. CCl_4/kgm. Each one receiving 7 cc. or more/kgm. died within twenty-four hours. Most of the others were killed after forty-eight hours. At autopsy all those that lived forty-eight hours showed translucent liver tracery. Those that died within twenty-four hours following administration presented no significant gross lesions; there were, however, hepatic coccidioidal cysts and abscesses in 60 per cent of the rabbits autopsied.

Microscopically, those receiving 7 cc. or more/kgm. show *no liver necrosis* (they died before it had time to develop). There is, in a few, some swelling and paleness of pericentral liver cells into which finely divided fat droplets have infiltrated. Among rabbits given less than 7 cc. CCl_4/kgm., 2 died within the first twenty-four hours and show no liver necrosis. However, all others receiving doses ranging from 0.1 to 6 cc./kgm. present central necrosis of the liver. It is interesting that this lesion occurs with the smallest dose (0.1 cc./kgm.) given. It is also quite striking that the amount of histological liver damage does not increase proportionately with the size of the dose administered. In some sections 90 per cent of the liver parenchyma is dead, leaving only a narrow band of live cells about portal radicles; in others not more than 30 to 40 per cent has been destroyed.

The odor of CCl_4 was frequently detected in rabbits' gastric and intestinal contents two days after the drug

had been given. This retention may explain in part the higher mortality among rabbits, and the presence of central necrosis of the liver following administration of such small doses of drug.

1. *Effect of administering paraffin oil with CCl_4.* A series of rabbits was given a lethal dose of CCl_4 with paraffin oil in various proportions, to determine the effect on toxicity as shown by the length of life. In the first 10 rabbits so treated there was a marked difference; 5 receiving 10 cc. CCl_4/kgm. died within fifteen hours; but 5 others receiving 10 cc. CCl_4/kgm. with 20 cc. paraffin oil/kgm. lived from twenty-two to fifty hours. At autopsy the latter 5 showed translucent liver tracery and microscopically extensive central hepatic necrosis. The experiments were continued; some 60 rabbits were used and it was determined rather conclusively that addition of paraffin oil has no striking effect on the toxicity of CCl_4. Lamson will report in detail on these experiments at a later date.

SUMMARY

Oral administration to adult dogs. After repeated massive doses, 25 cc. CCl_4/kgm., dogs died in from one to two and one-half weeks. One was jaundiced, the livers of each showed trabecular tracery. In sections, foci of hemorrhage and edema are found in the lungs; there is healing central necrosis of the liver with infiltration of an abundance of fat throughout most parenchymal cells. Periportal cells are relatively undamaged. Accumulations of albuminous material occur about some glomeruli.

In dogs killed after forty-eight hours, neither 0.01 cc./kgm. nor 0.05 cc./kgm. caused demonstrable lesions. With 0.1 cc./kgm. there is mild swelling and paleness of pericentral liver cells, a few fat droplets being found in them. 0.25 cc./kgm. intensified the previous lesion. After 0.5 cc./kgm., gross translucent trabecular liver tracery was seen; it is due to well-marked coagulative central necrosis. With 1 cc./kgm. neither gross nor microscopic lesions can be distinguished from the 0.5 cc./kgm. series. After 2 cc. CCl_4/kgm. the same lesions are found but more parenchyma is destroyed—two-thirds of the lobule is involved. After receiving 4 cc./kgm. one dog died in forty-eight hours, all showed gross liver tracery and sections reveal central necrosis of the liver. In one, albuminous fluid is found within Bowman's capsule.

Dogs killed several days after receiving 6 cc. CCl_4/kgm. show healing central necrosis quite like the 4 cc. series; one has foci of necrosis in the adrenal cortex. After 10 cc./kgm. 1 dog died in forty-eight hours, had gross liver tracery and microscopically extensive central necrosis.

Development and recession of liver lesions following 4 cc. CCl_4/kgm. After six hours there are no well marked changes; however, after twelve hours there was indistinct gross tracery and in sections the parenchymal cells about hepatic veins are swollen, stain palely and in places are actually necrotic. Periportal cells are unaffected. After twenty-four hours 1 dog presents a picture no farther advanced than after twelve hours, while another shows gross tracery. This is due to a coagulative necrosis of parenchymal cells

in the central two-fifths of the lobule. Between uninvolved periportal and necrotic central portions there is a zone of damaged liver cells full of fat. During the second day 1 dog died, all showed gross liver tracery, and microscopically the necrosis is well-marked. However, only parenchymal cells about the central vein are involved. Capillaries and Kupffer cells are nowhere damaged. In necrotic areas, individual cells are not distinct, and the nuclei are either pycnotic or fragmented. These necrotic areas stain a lustreless rose color in sharp contrast with live liver cells about portal radicles. These two zones are further differentiated by a zone of parenchymal cells laden with fat droplets. After four and five days gross tracery was less distinct and sections show that most dead cells have been removed by phagocytes. There remains, however, in central zones, a skeletal framework of intact capillaries and Kupffer cells. In a week all dead tissue is gone and only framework remains, resembling stellate scars between live liver cells, although no actual fibrous tissue is found. Kupffer cells are burdened with brown pigment and many parenchymal cells are hydropic. After two and three weeks nothing significant was found in the gross and no well-marked evidences of regeneration are seen. Collapsed areas about the central vein become smaller from week to week. After four and five weeks a few young budding liver cells can be seen pushing into the central regions between capillaries which act as a scaffold. Pigment-laden Kupffer cells persist and there is even yet some fat in parenchymal cells of the intermediate zone. Six cubic centimeters per kilogram did not intensify late healing liver lesions, nor did keeping 4 cc./kgm. dogs in low temperatures.

Effects of adding 4 cc. alcohol/kgm. Control dogs given alcohol alone, show no liver changes. There was no microscopic damage when it was given with 0.05 cc. CCl_4/kgm., but there was conspicuous increase in liver lesion when alcohol was given with 0.1 cc. CCl_4/kgm. With 4 cc. CCl_4/kgm. more dogs died and liver lesions after forty-eight hours are strikingly more extensive than in the dogs which did not receive alcohol. In healing stages no differences are found. However, when the amount of alcohol given with 4 cc. CCl_4/kgm. was reduced from 4 to 1 cc./kgm., fewer dogs died but liver lesions are histologically just as extensive. When given with 10 cc. CCl_4/kgm. there is no increase over the damage caused by 10 cc. CCl_4/kgm. without alcohol.

Effects of adding oily substances. When 20 cc./kgm. of cream was given before 4 cc. CCl_4/kgm., 1 of 8 dogs so dosed, died. Liver necrosis after forty-eight hours is more extensive but healing stages are not different from the straight 4 cc./kgm. series.

Four cubic centimeters of olive oil with an equal-sized dose of CCl_4/kgm. did not prove fatal to any of the dogs. Sections cannot be distinguished from the 4 cc. CCl_4/kgm. series.

In dogs given paraffin oil with CCl_4, liver lesions are not uniform. No dogs died. Sections are about like those found in dogs given a similar size dose of CCl_4 without paraffin oil. If there is any difference, it is too slight to be significant.

Inhalatation of vapor. After an exposure of an hour or longer to concentrated vapor, all dogs after two days or more showed central necrosis of the liver.

Intravascular injections. Peripheral vein injections of 0.154 cc. CCl_4/kgm. frequently resulted in death of dogs and were constantly attended by lung changes, consisting of foci of necrosis, hemorrhage and edema. These are almost entirely eradicated in a week. The liver is not damaged.

Intraportal injections of 0.154 cc. CCl_4/kgm. result in extensive hemorrhagic necrosis in the liver, death may follow, but if the dogs live, healing is well under way in three weeks.

Intracarotid injections of 0.154 cc. CCl_4/kgm. after an hour are attended by diffuse edema of cerebral meninges.

Subcutaneous injections. Only one dog was injected, a sterile abscess developed and on the third day translucent liver tracery was found, the result of well-marked central necrosis of the liver.

Intraperitoneal injections. All three dogs so treated had an effusion of bloody fluid in the peritoneal cavity and after twenty-four hours there is extensive central necrosis of the liver.

Rectal administration. Dogs given the drug per rectum and killed sixteen days later show healing central necrosis of the liver.

Puppies. After an oral dose of 4 cc. CCl_4/kgm., 50 per cent of the pups died, as contrasted with a death rate of 5 per cent in adult dogs. Livers all showed translucent trabecular tracery and microscopically, in most cases, the necrosis is extreme. It is similar to that seen in acute yellow atrophy. There is moderate cloudy swelling of convoluted tubular epithelium in the pups which died.

Rabbits. All given 7 cc. CCl_4/kgm. or larger doses died in less than twenty-four hours. Central necrosis of liver occurs with doses as small as 0.1 cc./kgm. and is found in all rabbits living twenty-four hours or longer. In many sections the lesion is extreme but the extent of the lesion does not vary directly with the size of the dose given. Addition of paraffin oil to a lethal oral dose of CCl_4 apparently does not prolong the rabbit's life.

DISCUSSION

Sources of error in oral administration of CCl_4. When CCl_4 is given to dogs by stomach tube, almost invariably they appear to be nauseated and may vomit at any time during the subsequent few hours. Consequently, unless they are watched closely, some drug may be lost and the experiments are vitiated. Furthermore, we have noticed that dogs receiving large doses of the drug may pass, after a few hours, gross CCl_4 in their stools. Dogs with diarrheal tendencies might expel most of the drug before appreciable absorption occurred. We feel that these two sources of error can account for the majority of discrepancies which have appeared in this communication.

Specificity of liver lesions following oral administration. Central necrosis of the liver, which we have found so uniformly after oral administration of large doses of CCl_4, is *not specific for this drug.* Similar hepatic lesions occur (16) in chronic passive congestion, in severe septicaemias, following inhalation of chloroform, and in acute yellow atrophy. Severe lesions found in puppies and in rabbits, as well as

following administration of alcohol with CCl_4 to adult dogs, simulate quite closely conditions of acute yellow atrophy.

Hydropic changes in liver cells. This is a condition, morphologically, in which parenchymal cells are swollen, stain palely, and the cytoplasm is reticulated, showing large, clear, empty spaces—like vacuoles (see Fig. 5). We can only speculate on the cause and significance of this condition; however these general statements should be added. The lesion apparently is not associated with administration of CCl_4; it occurs in controls and follows no recognizable schema in appearing after CCl_4 has been given. It is not caused by an infiltration of fat—Scharlach-R and Nile blue-sulphate stains are negative. The vacuoles or granules found in these cells do not seem to be composed entirely of glycogen, in so far as this substance can be demonstrated by Best's stain. There may, however, be some relationship, since hydropic livers contain much stainable glycogen whereas those containing little glycogen are not hydropic (17). Furthermore, the change does occur commonly in dogs given high carbohydrate diets (17). Since hydropic change appears so frequently in groups of dogs killed on the same day, regardless of treatment administered or elapsed time since dosing, we cannot escape feeling that either diet, amount of drug used to kill, or some peculiarity in fixatives employed, is responsible.

Kidney lesions following oral administration of CCl_4. 1. The streaks of cellular infiltration in both cortex and pyramids resemble human chronic pyelonephritis. Since similar areas of round and wandering cells are found beneath the mucosa of renal pelvis and bladder, they appear to be the result of an ascending renal infection, unrelated, obviously, to the administration of CCl_4.

2. Others (6) have made much of fat found in the lining cells of convoluted tubules and loops of Henle. We feel that there is no relation between this fat and the administration of CCl_4. It is such a common finding in healthy controls and, furthermore, in dogs receiving repeated massive oral doses, no fat was found in the kidneys, while in others killed after administration of very small doses, great accumulations of fat were found.

3. Accumulations of granular pink-staining material between Bowman's capsule and glomerular tufts are indicative of an albuminuria resulting from damage to the glomeruli.

4. Evidences of real nephritis appear no more frequently than would be found in any large series of dogs. furthermore, the lesion found could not possibly have advanced, within the time limits of our experiments, to the state of chronicity which our sections present.

Adrenal necroses following administration of CCl_4. Phelps and Hu (18) recently have reported adrenal necroses in a fatal human case of CCl_4 poisoning. Furthermore, the same lesions have been found by these authors in guinea-pigs after oral doses of CCl_4.

We have never been struck by the presence of adrenal lesions in our animals. However, since this communication (18) appeared, each one of the 170 adrenal sections in our files has been re-examined. In 2 cases

only do necroses occur; 1, a dog given 6 cc. CCl_4/kgm. by stomach tube and killed on the eleventh day; the other dog received an intraportal injection of 0.154 cc./kgm. and died after forty-eight hours. No sections from adrenals either of rabbits or puppies show necrosis.

Cathartic action of CCl_4. It has been observed frequently that the drug has a mild cathartic action on man. The same holds true for dogs, but is not the case with rabbits. Consequently, it is not surprising that rabbits die after smaller doses, show hepatic necroses with very small amounts of drug and more severe lesions with similar doses than do dogs.

The clinical enteritis which occurred in dogs receiving repeated massive oral doses probably is not specific for CCl_4 since it is well-known that, despite the etiological factor, sick dogs are prone to develop a terminal enteritis.

Anthelmintic properties of CCl_4. We want to emphasize that the efficacy of CCl_4 against hookworm infestation was not a part of our investigations. Furthermore, no efforts were made to recognize the presence of hookworm infection among our animals before dosing, nor were careful observations made on the passage of worms after dosing. However, it was noted that in *dogs receiving 0.05 cc. CCl_4/kgm., or larger oral doses, no hookworms were found at autopsy.* Forty per cent of our healthy adult controls were infested by hookworms. Furthermore, live hookworms were found at autopsy after inhalation of vapor, intravascular and intraperitoneal injections.

Smallest oral dose of CCl_4 which will produce liver necrosis. In our experiments oral doses of 0.01, 0.05, 0.1 and 0.25 cc. CCl_4/kgm. did not produce liver necrosis. More recently one of us, Wells, in a series of experiments on the absorption of CCl_4, has found liver necroses in dogs receiving from 0.176 to 0.375 cc. CCl_4 /kgm. It is apparent that many more observations will be necessary to determine accurately the smallest oral dose of CCl_4 which will produce liver necrosis.

CONCLUSIONS

1. Carbon tetrachloride causes central necrosis of the liver when (*a*) given by mouth, (*b*) the vapor is inhaled, (*c*) it is injected subcutaneously, or (*d*) intraperitoneally, and (*e*), it is administered per rectum.

2. Lesions, other than those found in the liver, are inconsequential after oral administration of CCl_4.

3. The smallest oral dose of CCl_4 which will produce liver necrosis has not been definitely determined. In our original series 0.5 cc. CCl_4/kgm., was the smallest, but more recently one of us has found necroses after doses of 0.176 cc. CCl_4/kgm.

4. Definite liver necrosis has been observed as early as twelve hours after oral administration of CCl_4. The maximum lesion occurs about forty-eight hours after dosage.

5. Healing of liver lesions begins three or four days after oral administration of CCl_4 and is not completed in five weeks.

6. The extent of the liver necrosis does not increase uniformly as the size of the oral dose of CCl_4 administered is increased.

7. Puppies are more susceptible to CCl_4 administered by stomach tube than are adult dogs.

8. Rabbits are more susceptible to CCl_4 administered by stomach tube than are adult dogs.

9. Simultaneous oral administration of alcohol with 4 cc. CCl_4/kgm. to adult dogs markedly increases the toxicity of CCl_4 as shown by the tremendous liver destruction and high death rate.

10. Oral administration of cream before 4 cc. CCl_4/kgm. does not greatly alter either the amount of liver destruction or the death rate.

11. Intraportal injections of CCl_4 produce only diffuse hemorrhagic liver necroses.

12. Injections of CCl_4 into a peripheral vein produce only foci of hemorrhage, edema and an occasional area of necrosis, in the lungs.

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Studies in Scarlet Fever

II. Studies on the Use of Convalescent Scarlet Fever Serum and Dochez' Scarlatinal Antistreptococcic Serum for the Treatment of Scarlet Fever[1]

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THE fact that one attack of scarlet fever renders most individuals immune to the disease, led Weisbecker (1) in 1897 to treat the severer cases of scarlet fever with the blood of persons convalescent from that disease. The results of numerous clinical trials with convalescent pooled serum were disappointing. During the following seven years, Leyden (2), Huber and Blumenthal (3), Scholtz (4) and many others repeated this form of serum treatment and then abandoned it. In 1912, with the advent of the Wassermann reaction, the method assumed renewed interest and was taken up by Reiss and Jungman (5), Koch (6), Weaver (7), Zingher (8), and other workers. These investigators made use of much larger doses of serum than had previously been administered (30 to 100 cc.) and the favorable results which they obtained with convalescent serum, particularly in severe cases, was encouraging. More recently Mironesco and Sager (9) at the *Colentina Hospital* at Bucharest, and Bernbaum (10) at the *Herman Kiefer Hospital* at Detroit have reported some success from the use of convalescent serum in severe cases of scarlet fever. The amount of serum administered varied from 10 to 35 cc. and was injected intramuscularly on the third to the eighth day of the disease. The blood was withdrawn from convalescents in the fourth to the fifth week of the disease, and the serum of several patients was mixed to make the final preparation. In the later report Bernbaum (10) stressed the importance of administering serum early and of using larger doses, varying between 50 and 100 cc.

Antistreptococcic serum in the treatment of scarlet fever was employed as early as 1895, when Marmorek (11) first attempted to immunize animals with polyvalent strains of streptococcus hemolyticus, isolated from the throats of scarlet fever patients. Numerous clinical trials with the Marmorek serum were disappointing, and its use was abandoned. Eight years later, Moser (12) prepared an anti-scarlatinal streptococcic serum by immunizing horses with strains of streptococcus hemolyticus isolated from the blood-stream of

[1] Read before the Medical Societies of the Johns Hopkins Hospital, May 19, 1924.

fatal and malignant cases of scarlet fever. Very promising results with this serum were reported by Schick (13) and numerous other observers. The Moser serum soon fell into disfavor in Central Europe because of the frequency with which it induced serum sickness. In Russia, however, it met with an enthusiastic reception and recently Aksenov (14) has reported 1335 cases treated with this serum. He concluded that the serum was of distinct benefit in the treatment of severe cases of scarlet fever and reduced the mortality about 25 per cent.

More recently, attempts to identify a specific strain of streptococcus hemolyticus as the cause of scarlet fever have been made by many workers. The researches of Bliss (15), Tunnicliffe (16), Stevens (17), Gordon (18), Dochez and Shermann (19), and Dochez (20) have demonstrated that the streptococcus hemolyticus, cultivated from the throats or secretions of patients suffering from scarlet fever does not differ culturally or morphologically from the streptococcus found in tonsillitis or other septic conditions. Serologically, however, the strain of streptococcus isolated from the throat secretions of scarlet fever patients differed from other strains, inasmuch as it was agglutinated by sera from animals immunized against streptococci obtained .from cases of scarlet fever, and not by sera obtained from animals immunized against strains of streptococci obtained from angina or other sources. Having established this fact, Dochez (20) immunized a horse with strains of this specific type of streptococcus hemolyticus, and succeeded in obtaining a serum which was capable of blanching locally the scarlet fever rash when injected intradermally in very small doses, and generally when injected subcutaneously in larger amounts. The observations made by Blake, Trask and Lynch (21) at New Haven indicated that the serum prepared by Dochez possessed specific therapeutic value in the treatment of severe instances of scarlet fever. Through the kindness of Dr. Dochez and under the direction of Dr. Amoss, the author was able to confirm the findings already published by Blake, Trask and Lynch (21) as regards the "rash extinction phenomenon" (22). The following study was made to determine the comparative value of (*a*) convalescent scarlet fever serum and (*b*) Dochez' scarlatinal antistreptococcic serum in the treatment of severe cases of scarlet fever.

THE USE OF CONVALESCENT SCARLET FEVER SERUM IN THE TREATMENT OF SCARLET FEVER

Blood was withdrawn from patients convalescing from scarlet fever in the third to the fifth week after defervescence of the fever. The blood from several patients was mixed, placed in the ice-box for 12 to 18 hours, the serum then drawn off, heated for an hour at 56°C. and stored in the ice-box in sealed bottles. To the bottles was added 0.3 per cent solution of tricresol. Sterility tests were made for every preparation of the serums. The blood Wassermann reactions of all patients were negative.

Thirty-seven patients with scarlet fever were treated during the first seven days of their disease with convalescent serum. The results of

TABLE I

Effect of convalescent scarlet fever serum in acute cases of scarlet fever

CASE	AGE	DAY OF DISEASE	NATURE OF DISEASE	DOSE OF SERUM	TEMPERATURE, PULSE AND RESPIRATION		RESULTS AND COMPLICATIONS
					Before injection	After 12 hours	
	Years			*cc.*			
4795	26	5	Severe	25	T. 104.0 P. 140 R. 32	99.4 110 28	Slight improvement after serum treatment. Relapse 20 hours later
		6		20	T. 104.1 P. 132 R. 24	100.2 98 24	Notable clinical improvement. Two days later general arthralgia. Recovery complete in 23 days
4797	15	3	Moderately severe	15	T. 101.2 P. 110 R. 22	98.4 100 18	Marked improvement after serum treatment. Sudden relapse with return of exanthem and angina on 17th day of disease
		17		25	T. 100.4 P. 130 R. 24	97.2 78 20	Temporary improvement during following three days. Sudden development of chills, nausea, vomiting and general arthritis. Blowing systolic murmur at apex
		21		25	T. 104.0 P. 130 R. 32	99.6 132 24	Slight clinical improvement during following two days. Sudden relapse associated with myocardial insufficiency
		23		25	T. 103.2 P. 136 R. 42	99.5 88 24	Temporary improvement during following two days. Development of bacterial endocarditis. Discharged on 52nd day of disease in poor physical condition
4802	5	3	Severe	20	T. 104.6 P. 160 R. 30	100.1 142 30	Marked temporary improvement after serum treatment. Development of cervical adenitis, chills and fever on seventh day of disease

		7		20	T. 103.8 P. 150 R. 42	101.0 120 34	Slow clinical improvement. Development of left otitis media on 21st day. Complete recovery by 49th day
4804	24	7	Severe	20	T. 102.8 P. 122 R. 28	99.8 80 20	Rapid clinical improvement during following 4 days. General arthritis on 15th day. Recovery complete on 21st day
4810	10	3	Severe	20	T. 102.6 P. 128 R. 32	98.8 100 20	Recovery in 6 days. No complication. Discharged on 21st day
4811	7	3	Severe	20	T. 101.0 P. 110 R. 28	99.2 102 24	Rapid improvement after serum treatment. Recovery complete by 9th day. Discharged on 21st day
4817	15	4	Mild	20	T. 101.8 P. 120 R. 28	99.4 104 20	Rapid improvement during following two days. Cervical adenitis on 18th day. Acute nephritis on 21st day. Recovery by 44th day of disease
4821	5	2	Severe	25	T. 103.4 P. 160 R. 32	99.0 94 22	Recovery on 4th day after serum treatment. No complication. Discharged on 22nd day
4822	5	2	Moderately severe	20	T. 103.6 P. 140 R. 30	99.6 130 24	Slow clinical improvement. Complete recovery by 12th day of disease. No complication. Discharged on 22nd day
4826	12	4	Moderately severe	20	T. 102.8 P. 124 R. 28	99.2 110 24	Recovery by 5th day after serum treatment. No complication. Discharged on 21st day
4868	27	4	Severe	20	T. 104.1 P. 120 R. 30	102.1 104 24	Prompt recovery by 4th day after serum treatment. No complication. Discharged on 21st day

TABLE I—*Continued*

CASE	AGE	DAY OF DISEASE	NATURE OF DISEASE	DOSE OF SERUM	TEMPERATURE, PULSE AND RESPIRATION		RESULTS AND COMPLICATIONS
					Before injection	After 12 hours	
	Years			*cc.*			
4869	4	11	Severe	20	T. 102.4 P. 148 R. 30	101.4 146 34	No clinical improvement. Development of suppurating tonsillitis and severe angina. Discharged on 28th day in poor physical condition
4885	6	2	Severe	20	T. 102.6 P. 120 R. 24	100.8 116 26	Complete recovery on 5th day. No complication. Discharged on 21st day
4908	2	3	Moderately severe	20	T. 102.8 P. 108 R. 22	99.8 124 28	Complete recovery on 4th day. Mild attack of cervical adenitis on 13th day. Recovered and discharged on 27th day
4910	9	6	Mild	20	T. 103.0 P. 148 R. 30	99.1 132 26	Recovered on 5th day after serum treatment. No complication. Discharged on 21st day
4914	23	4	Moderately severe	25	T. 103.6 P. 130 R. 32	101.6 116 24	Slight improvement after serum treatment. Cervical adenitis and arthritis on 9th day. Recovery by 24th day
4916	11	2	Mild	20	T. 103.0 P. 118 R. 24	100.2 110 24	No improvement after serum treatment. Arrhythmia and tachycardia until 34th day. Recovery by 38th day
4919	6	2	Mild	20	T. 103.4 P. 134 R. 30	100.2 124 26	Rapid improvement within 24 hours. No complication. Recovery complete by 6th day

4926	4	4	Mild	20	T. 102.2 P. 112 R. 30	99.6 116 22	Persistent angina until 9th day. Acute rhinitis and otitis media on 23d day. Recovery by 30th day
4932	4	2	Moderately severe	20	T. 103.2 P. 130 R. 34	100.4 100 24	Slow clinical improvement. Acute rhinitis on 21st day. Recovery by 31st day
4933	9	2	Severe	20	T. 104.8 P. 148 R. 30	102.2 140 24	No clinical improvement after serum treatment. Angina and fever persisting
		5		35	T. 103.6 P. 142 R. 32	102.4 160 40	No clinical improvement. Development of myocardial insufficiency and acute nephritis on 24th day. Discharged on 57th day in poor condition
4935	6	3	Severe	20	T. 104.0 P. 150 R. 40	102.1 142 38	Slow improvement after serum treatment. Cervical adenitis and suppurating tonsillitis on 4th day. Recovery by 16th day
4936	8	2	Moderately severe	25	T. 104.4 P. 158 R. 40	101.2 154 32	Slow improvement after serum treatment. Cervical adenitis and acute pharyngitis on 23d day. Recovery by 35th day
4925	3	4	Severe	20	T. 104.1 P. 130 R. 40	100.8 120 28	Slow improvement after serum treatment with sudden relapse on second day of chills, nausea and fever
		6		30	T. 104.0 P. 170 R. 38	103.1 140 36	No clinical improvement. Double otitis media on 9th day; pyelitis on 24th day. Otitis persisted more than 90 days Discharged in poor condition on 92nd day of disease
4981	12	3	Severe	20	T. 103.4 P. 160 R. 30	101.2 136 22	Slow improvement after serum treatment. Double otitis media on 8th day. Otorrhea ceased on 52nd day of disease. Discharged on 53d day

TABLE I—*Continued*

CASE	AGE	DAY OF DISEASE	NATURE OF DISEASE	DOSE OF SERUM	TEMPERATURE, PULSE AND RESPIRATION		RESULTS AND COMPLICATIONS
					Before injection	After 12 hours	
	Years			*cc.*			
4989	25	9	Moribund	20	T. 104.1 P. 130 R. 40	101.6 134 36	Slight clinical improvement during 18 hours after serum treatment. Development of chills and vomiting. Streptococcal septicemia: 16 colonies per cc. of blood
		10		20	T. 104.8 P. 136 R. 34	102.4 134 24	No clinical improvement. Died
4992	4	2	Severe	20	T. 103.4 P. 160 R. 34	100.2 110 24	Slow clinical improvement after serum treatment. Cervical adenitis on 4th day; general arthritis and multiple axillary abscesses on 19th day. Recovery by 47th day
5011	7	2	Severe	20	T. 103.8 P. 148 R. 40	99.2 110 24	Rapid improvement after serum treatment. General arthritis on 10th day. Recovery by 21st day
5019	20	3	Severe	20	T. 102.4 P. 150 R. 32	100.2 120 24	Rapid improvement within 36 hours after serum treatment. No complication. Discharged on 21st day
5028	15	2	Severe	25	T. 102.2 P. 122 R. 24	99.2 100 20	Striking clinical improvement within 24 hours after serum treatment. No complication. Discharged on 21st day
5077	25	3	Malignant	25	T. 105.2 P. 140 R. 38	104.8 148 34	No clinical affect. Succumbed 23 hours after admission. Septicemia and lobar pneumonia
5056	8	1	Moderately severe	25	T. 102.4 P. 110 R. 22	99.0 110 20	No clinical improvement after serum treatment. Angina, chills and fever persisting
		2		20	T. 102.6	99.4	Marked clinical improvement during 24 hours, with sudden

					R. 22	20	chills and fever persisting
		2		20	T. 102.6 P. 118 R. 22	99.4 100 20	Marked clinical improvement during 24 hours, with sudden relapse of chills and fever
		3		15	T. 102.0 P. 116 R. 26	98.2 80 24	Slow improvement. Left otitis media developed on 10th day general arthritis on 15th day. Recovery by 22nd day
5029	4	2	Severe	30	T. 105.0 P. 156 R. 36	102.2 160 24	Slight improvement in comatose condition; angina increasing in severity and rash is deepening in color
		3		25	T. 104.4 P. 160 R. 36	103.6 160 34	No clinical improvement. Development of acute rhinitis and cervical adenitis
		4		20	T. 104.2 P. 156 R. 32	104.6 160 34	Slow improvement. Myocardial insufficiency and acute nephritis on 22nd day. Fair recovery by 36th day
5031	5	1	Severe	35	T. 103.0 P. 148 R. 28	100.4 120 24	Rapid improvement of toxic depression. Persistent angina and fever
		2		20	T. 102.1 P. 134 R. 30	99.8 100 28	Marked clinical improvement after serum treatment. Mild attack of rhinitis on 12th day. Recovery by 18th day
5106	9	2	Severe	20	T. 104.1 P. 146 R. 30	102.0 130 28	Rapid clinical improvement 24 hours after serum treatment. No complication. Recovery by 6th day
5115	16	2	Severe	20	T. 104.2 P. 130 R. 30	100.2 120 24	Slow improvement in febrile condition. Recovery by 7th day. No complication
5203	4	2	Severe	20	T. 104.2 P. 134 R. 30	103.0 126 26	No clinical improvement after serum treatment. Development of pyelitis on 7th day. Recovery by 28th day

these treatments are shown in brief outline in Table I. All of the severe cases presented hyperpyrexia, tachycardia, intense exanthem and marked leucocytosis. Two cases were of the malignant type, 15 cases were considered severe, 15 patients were moderately ill and 5 cases were mild. Of the total 37 cases, 26 were in children and 11 in adults. The average dose administered was 20 cc. of convalescent serum and it was always given intramuscularly. The largest amount of serum given one patient was 85 cc. and the smallest was 15 cc. In only nine cases was more than one dose administered. These patients were extremely ill. In the presence of septic complications it was noted that the general course of the disease was not greatly altered by the serum treatment, although there was constantly observed a rapid abatement in the toxemia and a slight drop in the temperature, pulse and respiration rate. This improvement was not always sustained and repeated doses of the serum failed to avert septic complications.

The most striking clinical improvement occurred when the patients, irrespective of the degree of toxemia, were treated before the fourth day of the disease. In the absence of complications, these patients showed immediate improvement following the intramuscular injection of doses varying from 20 to 35 cc. of the serum. Temporary improvement occurred in some cases as early as two hours after the administration of serum. There was appreciable improvement twelve hours after the injection of serum, and in this series of 37 cases, besides a definite decrease of toxemia, there was an average drop in temperature of 2.8°F. and a decrease in pulse rate of 16 beats per minute. The leucocytosis diminished from an average of 20,000 to 14,000 cells within twelve hours following the serum therapy, and there was a return to the average normal proportions of the polymorphoneutrophiles and lymphocytes within seven to ten days in uncomplicated cases. No appreciable reduction in the rash extinction time was noted as a result of this form of therapy, and the course of albuminuria and cylindruria differed but little from that of the average untreated severe case of scarlet fever.

Satisfactory recovery without complications was observed in thirteen of the thirty-seven cases treated with convalescent scarlet fever serum, or in 35 per cent. Twenty-two patients (59 per cent) showed temporary improvement; although complications developed and prolonged their convalescence, eventually they recovered and were discharged in good physical condition. Two patients, (6 per cent), moribund on admission, died from streptococcus beta hemolyticus septicemia.

Bearing in mind that this series of 37 cases included only the severer instances of scarlet fever, it is of interest to note the high incidence of septic complications. In their order of frequency there occurred cervical adenitis in 7 cases (19 per cent); arthritis in 7 cases (or 19 per cent); suppurative otitis media in 5 cases (13 per cent); rhinitis and myocarditis in 4 cases each (11 per cent); nephritis in 3 cases (8 per cent); endocarditis, pyelitis and septicemia, two cases of

each (5 per cent); suppurating axillary abscesses, pharyngitis, suppurating tonsillitis and lobar pneumonia, one case of each, (3 per cent). No case of serum sickness occurred.

Brief case reports of three cases treated with convalescent scarlet fever serum follow:

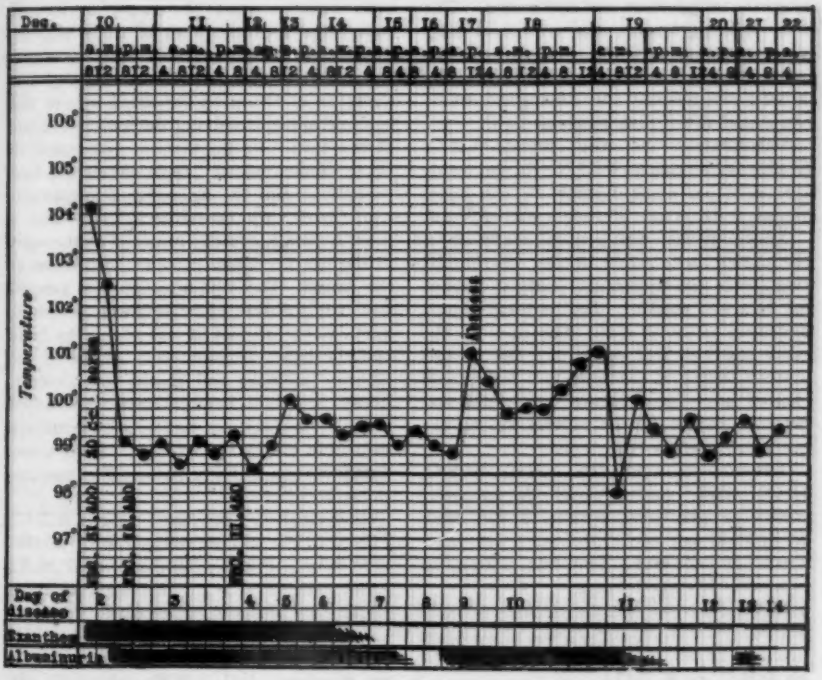

FIG. 1. COURSE OF TEMPERATURE IN CASE 1, ADMITTED ON SECOND DAY OF SCARLET FEVER

Case 1. B. J., a girl, aged 4, was admitted to the Sydenham hospital on December 10, 1923, about thirty hours after the appearance of the rash. She was moderately ill, prostrated, vomited frequently and showed extensive stomatitis. There was marked injection and hyperemia of the faucial ring, and the uvula presented an irregular necrotic process involving the left portion of the soft palate. Numerous white plaques were seen on both tonsils. The cervical glands were greatly enlarged firm and matted together. The rash was deep red, showing punctate hemorrhages with large areas of inflammatory edema in the dependent portions of the back. Minute miliary sudamina were seen about the axillae. Mentally, the patient was very drowsy and uninterested in her surroundings. Temperature 101.2°F., pulse 148, respirations 40.

Examination of the blood: R.B.C. 4,356,000; Hb. 87 per cent; W.B.C. 31,400. Diff. count: P.M.N. 89 per cent; P.M.E. 2 per cent; P.M.B. 0 per cent; Lymph. 3 per cent; Monos. 4 per cent; Myelocytes 3 per cent. Platelets almost absent.

Urine: deep amber, turbid, acid; S.G. 1034; albumin, ++; urobilin, strongly positive; numerous coarse granular casts; a few R.B.C. and W.B.C.

On December 10, at 8:15 a.m., 30 cc. of

convalescent scarlet fever serum were injected intramuscularly.

On December 10, at 8 p.m. there was noted a striking improvement in the patient's general condition. She sat up in bed and conversed with her fellow-patients. The face was not flushed and the color of the mucous membranes seemed pale. No recession was noted in the vividness of the scarlet erythema, and the only perceptible change in the stomatitis was a lessened intensity in injection and hyperemia. The most striking feature was a critical drop in temperature to 99.0°F., a fall in pulse-rate to 110 and in respirations to 24. The patient vomited only once during the twelve hours and after that retained fluids.

Examination of the blood: W.B.C. 16,480. Diff. count: P.M.N., 76 per cent; P.M.E. 2 per cent; Lymph. 18 per cent; Monos. 4 per cent. Platelets still reduced.

December 11. The general condition of the patient was much better, the faucial ring clean and apparently normal, except for enlarged tonsils. The cervical glands had diminished in size. The rash on the arms and legs had faded and the inflammatory edema of the back had completely cleared up. Temperature, pulse and respiration had remained normal during the preceding twenty-four hours.

Examination of the blood: W.B.C. 11,460. Diff. count: P.M.N., 58 per cent; P.M.E. 3 per cent; P.M.B. 1 per cent; Lymph. 32 per cent; Monos. 2 per cent; Trans. 4 per cent. Platelets normal in number. No myelocytes.

Urine: straw-colored and clear, of acid reaction; S.G. 1018; slight trace of albumin; urobilin, negative; occasional cellular casts; no R.B.C. or W.B.C.

The blood culture showed no growth of bacteria in 2 cc. of the patient's blood after 48 hours' incubation.

The general condition remained satisfactory until December 18, when large axillary abscesses formed. The following week myocarditis developed. On January 26, 47 days after admission to the hospital, the patient was discharged in good condition.

Case 2. H. H., a girl, aged 4, was admitted to the Sydenham Hospital on December 31, 1923, about forty hours after a sudden attack of nausea, profuse and persistent vomiting, sore throat, diarrhea and fever, and thirty hours after the initial appearance of the rash. On admission she was in a semi-comatose condition, deeply cyanosed, with profuse seropurulent conjunctival discharge and tenacious muco-purulent nasal discharge. A heavy greenish-white, pultaceous membrane extended from the soft palate, over both tonsils, towards the naso-pharynx and obstructed a proper view of these organs. The cervical glands were greatly enlarged and matted together. Inflammatory induration of the neck extended across the mastoid areas, involving the lower portions of the ears. No fluctuation was noted in these swollen parts. Both ear-drums had perforated and the discharge was creamy-white and very tenacious. There was a loud, blowing, systolic murmur at the apex of the heart. Moist râles at both bases of the lungs. The skin presented a general and evenly diffuse strawberry-red exanthem particularly intense on the arms, the back and the legs. Inflammatory edema of the elbows, buttocks and thighs was present. Many petechial hemorrhages were noted in the folds of the skin and numerous miliary sudamina about the axillae and on arms. Temperature, 104°F.; pulse, 156; respirations, 36.

Examination of the blood: R.B.C., 3,920,000; Hb., 82 per cent; W.B.C., 25,000. Diff. count: P.M.N., 78 per cent; P.M.E., 1 per cent; P.M.B., 0 per cent; Lymph., 17 per cent; Monos., 4 per cent. Platelets almost absent.

The urine was deep amber, turbid, acid in reaction; S.G., 1020; albumin, +; urobilin, positive. Microscopically: numerous coarse, granular casts; many W.B.C. and a few R.B.C.

December 31, 10 p.m. The patient's condition appeared hopeless and the cyanosis had deepened. The temperature had increased to 104.8. and the pulse to 160. Thirty cubic centimeters of convalescent scarlet fever serum were given intramuscularly at 10:15 p.m.

On January 1, 8 a.m. (ten hours following serum injection), the patient was resting quietly. She answered, when ad-

dressed, in a sluggish, drowsy manner, complaining of intense headache and general itching. Her physical condition presented no striking change. The temperature had fallen to 102°, but the pulse persisted at 160. There was little evident improvement.

At noon the temperature rose to 105.1°, the cyanosis deepened and chills became frequent. Impending death seemed inevitable. At 11:30 p.m., another dose (15 cc.) of convalescent scarlet fever serum was given intramuscularly.

Examination of the blood: R.B.C., 3,645,000; Hb., 78 per cent; W.B.C., 22,360. Diff. count: P.M.N., 89 per cent; P.M.E., 6 per cent; P.M.B., 0 per cent; Lymph., 2 per cent; Monos., 3 per cent. Platelets almost absent.

The urine was brownish-red and turbid, acid in reaction, S.G., 1034; albumin, ++; urobilin, strongly positive. Microscopically; abundance of coarse, granular casts; many W.B.C. and R.B.C.

The blood-culture showed no growth of bacteria in 2 cc. of the patient's blood after 48 hours' incubation.

On January 2, there was no change in the physical condition of the patient. Vomiting, chills and diarrhea were frequent and acute urinary retention developed. The average temperature during the past 24 hours was 104°F. At 3:30 p.m., a third dose of convalescent scarlet fever serum (20 cc.) was given intravenously. There was no immediate untoward effect. No perceptible change in the patient's general condition was noted. The temperature varied between 103.6° and 104.8° during the following four days. Acute nephritis developed on the eighteenth day of the disease, albumin, blood and casts being

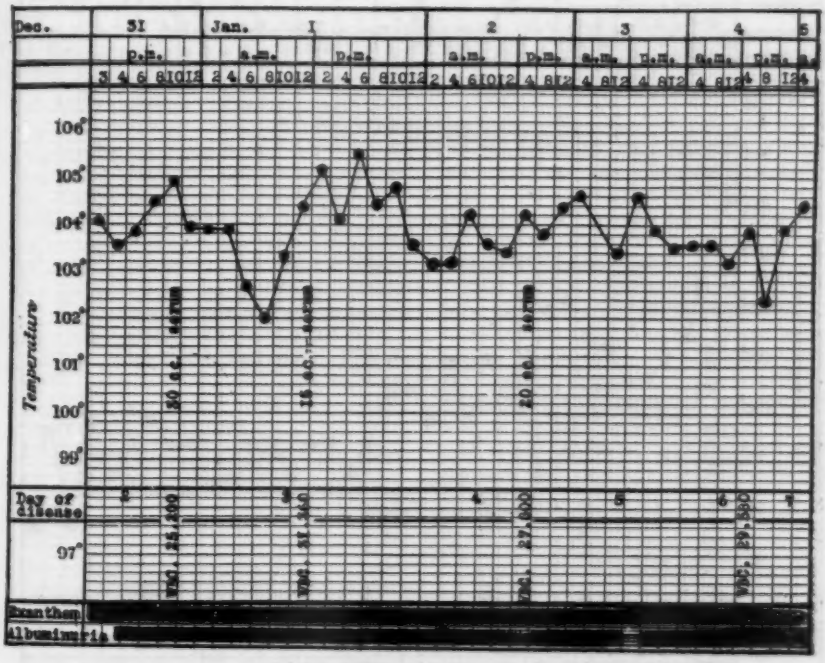

FIG. 2. COURSE OF TEMPERATURE IN CASE 2, ADMITTED ON SECOND DAY OF SCARLET FEVER

found in the urine. The duration of the attack was 36 days, after which the patient was discharged in very poor physical condition.

Case 3. D A., a girl, aged 5, admitted to the Sydenham hospital on January 2, 1924, about twenty-four hours after the appearance of the rash. She was very ill, with a thick, greenish-white membrane. Small areas of necrosis were seen bilaterally at the junction of the uvula and the tonsils. The tongue was furred in the center and red along the edges, the papillae were prominent and deeply injected. The cervical glands were enlarged on both sides, matted together and very tender to pressure. The marked induration of the tissues

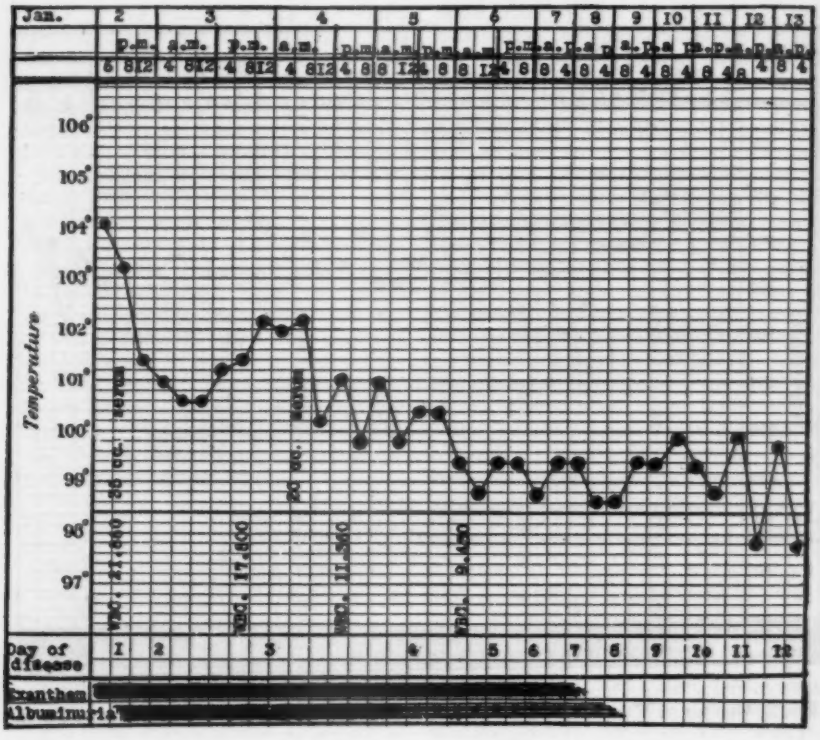

FIG. 3. COURSE OF TEMPERATURE IN CASE 3, ADMITTED ON FIRST DAY OF SCARLET FEVER

drowsy and apathetic. The face was flushed and scaly; the conjunctivae were deeply injected and discharged a seropurulent fluid; the nose was crusted and the nasal discharge profuse. A heavy, brownish film coated the lips, teeth, gums and the floor of the mouth. The tonsils and the palate were swollen and covered of the neck suggested beginning cellulitis. The exanthem was general, papular in type and purplish-red in color. Over the extremities the rash appeared blotchy. Prognosis doubtful. Temperature 104.1°; pulse, 140; and respirations, 28.

Examination of the blood: R.B.C., 3,896,000; Hb., 85 per cent; W.B.C., 31,860.

Diff. count; P.M.N., 64 per cent; P.M.E., 0 per cent; Lymph., 32 per cent; Monos., 4 per cent. Platelets greatly reduced.

The urine was dark amber in color, turbid, strongly acid in reaction; S.G., 1022; albumin, +; urobilin, strongly positive. Microscopically; numerous cellular casts, many W.B.C. and occasional R.B.C.

On January 2, at 8:30 p.m., the temperature was 103°; pulse, 148; respirations, 28. The patient was delirious and very restless. At 8:45 p.m., 35 cc. of convalescent scarlet fever serum were given intramuscularly.

On January 3, at 9 a.m. (twelve hours following the serum injection), some clinical improvement had occurred. The patient inquired about her surroundings and begged for food. Otherwise there was no apparent change. The angina was painful and swallowing very difficult. The patient vomited only once during the night and had no chills. The most striking change was the drop in temperature to 100.4°, in pulse to 120, and the respirations were less labored.

Examination of the blood: W.B.C., 17,800. Diff. count: P.M.N., 75 per cent; P.M.E., 4 per cent; P.M.B., 0 per cent; Lymph., 9 per cent; Monos., 8 per cent; Trans., 4 per cent. No myelocytes. Platelets increasing in numbers.

On January 4, the patient's general condition was distinctly improved, but only a very slight abatement in the intensity of the rash and the angina had occurred. Swallowing was less painful. The cervical glands were smaller in size and the inflammatory condition of the neck showed some recession. The temperature rose during the night to 102.1° and the pulse to 134. At 8 a.m., 20 cc. of convalescent scarlet fever serum were given intramuscularly.

At 8 p.m. (twelve hours following serum injection), the temperature had fallen to 99.6°; the pulse, to 100. The palate and tonsils were less swollen and the membrane was readily removed. The cervical glands were smaller in size and not tender to pressure. Swallowing was less difficult and only moderately painful. The rash was less intense in color.

Examination of the blood: W.B.C., 11,360. Diff. count: P.M.N., 65 per cent; P.M.E., 3 per cent; P.M.B., 2 per cent; Lymph., 17 per cent; Monos., 9 per cent; Trans., 2 per cent; Myelocytes, 2 per cent. Platelets normal.

The urine was dark amber in color, strongly acid, S.G., 1024; albumin, negative; urobilin, negative. Microscopically: occasional granular casts and a few W.B.C. and R.B.C.

The blood-culture taken on January 2nd and 3rd yielded no growth of bacteria after 48 hours' incubation.

On January 6, the patient's general condition was distinctly improved; she was playful, active and mentally alert. The tonsils and faucial ring showed slight swelling and injection, while the mucous membranes were clean and free from membrane. The angina and edema of the neck had receded and the rash had faded slightly. The temperature, pulse and respirations were within normal limits.

Examination of the blood: W.B.C., 9430. Diff. count: P.M.N., 58 per cent; P.M.E., 6 per cent; Lymph., 24 per cent; Monos., 8 per cent; Trans., 2 per cent; Myelocytes, 2 per cent. Platelets normal.

The patient has remained well and developed no complications, except for a mild attack of acute rhinitis, which disappeared four weeks after admission to the hospital.

THE USE OF DOCHEZ' SCARLATINAL ANTISTREPTOCOCCIC SERUM IN SEVERE AND ACUTE CASES OF SCARLET FEVER

As it has been established that Dochez' scarlatinal antistreptococcic serum causes the rash extinction phenomenon of the exanthemata of scarlet fever patients in a more striking manner than the serum of convalescent scarlet fever patients or than normal human serum, it seemed important to compare the therapeutic value of these sera.

Thirty cases of scarlet fever were treated within the first four days of

TABLE II

Effect of Dochez' scarlatinal antistreptococcic serum in thirty acute cases of scarlet fever

CASE	AGE	DAY OF DISEASE	NATURE OF DISEASE	DOSE OF SERUM	TEMPERATURE, PULSE AND RESPIRATION		LEUCOCYTOSIS		RESULTS AND COMPLICATIONS
					Before injection	After 12 hours	Before injection	After 12 hours	
	Years			*cc.*					
M. B.	9	2	Very toxic	40	T. 103.6 P. 130 R. 30	99.8 80 24	36.160	10.400	Rapid improvement in toxemia; rash disappeared completely in 12 hours after serum treatment. Recovery complete by third day. No complications
D. G.	33	3	Hemorrhagic S. F.; very toxic	40	T. 103.1 P. 110 R. 34	98.6 88 18	24.400	11.150	Toxic manifestations relieved eight hours after serum treatment. Rash had disappeared completely 24 hours after serum treatment. Left otitis media developed on 6th day. Complete recovery by 12th day
A. N.	39	2	Severely toxic	40	T. 103.6 P. 136 R. 38	98.4 84 22	29.200	10.200	General physical condition rapidly improved and rash faded completely 9 hours after serum treatment. Serum sickness developed on 7th day. No septic complication. Complete recovery by 9th day
R. F.	10	4	Streptococcus septicemia; moribund	35	T. 104.8 P. 150 R. 50	108.0 168 22	7.200		No effect of serum treatment. Patient died 12 hours after admission
I. P.	39	3	Moderately toxic; hemorrhagic exanthem	40	T. 101.2 P. 120 R. 28	98.4 78 16	20.800	11.400	Notable clinical improvement, with complete rash extinction twelve hours after serum treatment. Recovery by 3d day. No complications
R. G.	13	3	Very toxic	40	T. 104.2 P. 136 R. 28	98.4 100 22	32.460	14.350	General physical condition strikingly improved twelve hours after serum treatment. Rash faded completely in 36 hours. Pyelitis developed on 6th day. Recovery complete by 12th day

F. S.	25	2	Very toxic	25	T. 104.2 P. 120 R. 50	103.6 108 42	23.800	7.960	Temporary clinical improvement during 16 hours after serum treatment. Lobar pneumonia developed; patient fell into coma and died 20 hours after serum treatment
M. K.	21	3	Moderately toxic	80	T. 103.8 P. 136 R. 28	99.6 98 18	32.600	11.560	Marked clinical improvement 12 hours after serum treatment; rash faded completely within 16 hours. Serum sickness developed on 5th day. Recovery complete by 7th day. No complications
B. R.	27	2	Moderately toxic	40	T. 103.8 P. 124 R. 28	99.6 98 20	26.400	13.560	Rapid clinical improvement within 8 hours and rash faded completely 22 hours after serum treatment. Recovery complete by 3d day. No complications
C. L.	25	1	Very toxic	60	T. 104.4 P. 128 R. 30	98.8 100 16	22.300	14.400	Marked improvement within 8 hours and rash faded completely 12 hours after serum treatment. Serum sickness on 5th day. Recovery complete by 7th day. No complications
M. S.	10	1	Moderately toxic	10	T. 102.5 P. 116 R. 28	100.6 98 24	28.600	25.460	Notable clinical improvement 6 hours after serum treatment; rash faded completely within 11 hours. Five hours later sudden relapse with chills, nausea vomiting and return of rash
		2		15	T. 102.6 P. 160 R. 36	99.0 110 24	33.750	13.480	Definite clinical improvement 8 hours after second dose of serum; rash faded within 10 hours. Complete recovery by 4th day. No complications
F. B.	5	1	Moderately toxic	25	T. 103.4 P. 120 R. 28	100.1 98 18	21.430	14.600	Rapid improvement in toxic manifestations within 12 hours; rash had faded completely 16 hours after serum treatment. Sudden relapse 14 hours later with return of nausea, vomiting, chills and rash
		2		40	T. 103.8 P. 120 R. 28	99.6 110 24	21.860	12.600	Symptoms subsided completely within 8 hours after second dose of serum; rash faded within 12 hours. Recovery complete by 4th day. No complications

TABLE II—*Continued*

CASE	AGE	DAY OF DISEASE	NATURE OF DISEASE	DOSE OF SERUM	TEMPERATURE, PULSE AND RESPIRATION		LEUCOCYTOSIS		RESULTS AND COMPLICATIONS
					Before injection	After 12 hours	Before injection	After 12 hours	
	Years			*cc.*					
M. W.	10	1	Very toxic	40	T. 103.2 P. 138 R. 32	99.8 106 22	26.600	15.600	Rapid clinical improvement within 8 hours and rash faded completely 9 hours after serum treatment. Recovery complete by 3d day. No complications
G. B.	12	1	Moderately toxic	40	T. 104.2 P. 142 R. 26	99.7 90 18	29.300	11.240	Rapid clinical improvement within 12 hours; rash had faded completely 16 hours after serum treatment. Recovery complete by 4th day. No complications
B. F.	5	7	Mildly toxic. Extreme cervical adenitis	25	T. 102.8 P. 150 R. 34	99.6 100 24	23.200	11.640	Clinical improvement marked with 12 hours; rash had faded completely 14 hours after serum treatment Recovery complete by 4th day. No complications
S. A.	27	2	Moderately toxic	40	T. 104.4 P. 128 R. 30	98.4 96 24	22.240	13.580	Greatly relieved within 8 hours; rash had faded completely 12 hours after serum treatment. Recovery complete by 3d day. No complications
J. W.	14	3	Very toxic	40	T. 102.4 P. 134 R. 28	100.0 96 20	26.200	14.360	Marked improvement within 8 hours; rash had faded completely 14 hours after serum treatment. Angina subsided on 3d day. Serum sickness and general arthritis developed on 6th day. Recovery complete by 12th day. No further complications
D. W.	21	3	Malignant, hemorrhagic S. F.; septicemia	40	T. 104.8 P. 146 R. 36		36.400		Moribund condition on admission. Intravenous injection of serum followed by brief circulatory improvement. Died 3 hours later. *Streptococcus beta hemolyticus*, 64 colonies per cc. of blood

H. B.	11	2	Moderately toxic	40	T. 103.4 P. 124 R. 26	99.6 98 22	26.880	11.300	General condition greatly relieved within 10 hours; rash had faded completely 13 hours after serum treatment. Angina resolved on the second day. Serum sickness developed on the 8th day. Recovery complete by 10th day. No complications
C. R.	4	3	Very toxic	40	T. 104.2 P. 140 R. 32	100.4 108 24	21.800	12.400	General improvement within 10 hours; rash had faded completely 20 hours after serum treatment. Recovery complete by 4th day. No complications
L. H.	8	2	Very toxic	40	T. 104.1 P. 130 R. 30	99.2 92 22	23.600	14.830	Marked improvement 5 hours after serum treatment. Rash faded completely within 18 hours. Recovery complete by 4th day. No complications
R. G.	8	2	Mildly toxic	40	T. 101.6 P. 134 R. 30	99.0 110 20	13.600	7.640	General improvement within 6 hours; rash had faded completely 10 hours after serum treatment. Recovery complete by 3d day. No complications
E. B.	6	2	Moderately toxic	40	T. 103.4 P. 160 R. 30	99.0 120 22	16.300	10.360	Much relieved within 8 hours. Rash had faded completely 16 hours after serum treatment. Recovery complete by 3d day. No complications
D. M.	II	3	Very toxic	40	T. 103.1 P. 120 R. 32	100.1 98 20	26.540	14.800	Toxic symptoms markedly reduced within 12 hours; rash had faded completely 24 hours after serum treatment. Cervical adenitis and acute rhinitis resolved on 5th day. Recovery complete by 7th day. No further complications
H. R.	2	2	Severe	40	T. 104.8 P. 168 R. 34	98.8 100 22	26.800	19.600	Much relieved within 12 hours; rash had faded completely 16 hours after serum treatment. Recovery complete by 3d day. No complications
S. F.	7	1	Moderately severe	40	T. 104.0 P. 140 R. 34	100.6 120 22	23.800	13.360	Marked improvement in toxic symptoms within 10 hours; rash had faded completely 16 hours after serum treatment. Sudden development on 3d day of tachycardia and high fever, associated with frequent chills, nausea and vomiting

TABLE II—*continued*

CASE	AGE	DAY OF DISEASE	NATURE OF DISEASE	DOSE OF SERUM	TEMPERATURE, PULSE AND RESPIRATION		LEUCOCYTOSIS		RESULTS AND COMPLICATIONS
					Before injection	After 12 hours	Before injection	After 12 hours	
	Years			*cc.*					
		3	Moderately severe	40	T. 104.1 P. 136 R. 24	102.6 110 20	21.400	18.860	Repeated serum treatment. Slight response in reduction of temperature and tachycardia. Serum sickness developed on 5th day. Recovery complete by 8th day. No septic complications
A. M.	8	2	Severe	40	T. 104.8 P. 136 R. 28	98.5 110 22	19.240	11.600	General improvement within 8 hours; rash had faded completely 10 hours after serum treatment. Angina severe for 3 days. Recovery complete by 6th day. No complications
D. C.	9	2	Moderately severe	40	T. 104.1 P. 144 R. 28	99.2 110 20	31.460	16.400	Marked improvement within 12 hours; rash had faded completely 16 hours after serum treatment. Serum sickness developed on 5th day. Recovery complete by 8th day. No complications
S. R.	4	2	Severe	40	T. 104.4 P. 136 R. 28	99.6 100 32	26.100	15.300	Moribund on admission. Severe form of scarlet fever complicated with nasal, pharyngeal and laryngeal diphtheria. Much relieved within 12 hours; rash faded 26 hours after serum treatment. Serum sickness developed on 5th day. Recovery complete by 10th day. No septic complications
J. M.	5	4	Severe	40	T. 103.1 P. 140 R. 30	99.0 92 24	17.800	11.400	Much relieved within 9 hours; rash had faded completely 14 hours after serum treatment. Recovery complete by 3d day. No complications

the disease with Dochez' serum, and one case on the seventh day of the disease. Of these 31 patients, 16 were children and 15 adults. Three patients were moribund on admission; 15 cases were severe; 11 cases were moderately severe and 2 cases were mild. Six patients were treated on the first day of the disease; 13 on the second day; 9 on the third day; 2 on the fourth day, and 1 on the seventh day of the disease. In most instances, a sensitization skin-test was performed with the serum previous to the injection of the therapeutic dose and found to be negative. In 17 cases the rash extinction phenomenon was demonstrated prior to the administration of the therapeutic dose of therapeutic serum and in every instance this test was positive. The average dose of serum injected intramuscularly was 40 cc. The largest dose administered to one individual was 80 cc. and the smallest was 10 cc. The results of these treatments are shown in Table II. In an effort to standardize the dose of serum necessary to produce a definite clinical improvement in moderately severe cases, experiments were conducted with doses varying from 10 to 80 cc. Cases 8 and 9 were studied from this point of view. Both patients presented the average picture of moderately severe scarlet fever with an intense exanthem. These cases will be discussed later.

The dominant effect which usually followed the injection of serum was a prompt improvement in the symptoms of toxemia. Then followed a sudden and almost critical drop in the temperature which took place in from eight to twelve hours after injection. The fall in temperature was accompanied by a drop in the rate and improvement in the quality of the pulse. Not less striking was the sudden disappearance of the rash, which occurred twelve to twenty hours after the injection and the rapid decrease within 30 to 60 hours in the leucocytosis with return of polymorphonuclear neutrophiles, eosinophiles and lymphocytes to normal proportions. Albuminuria and cylindruria decreased within 24 to 48 hours. In the cases with septicemia and pneumonia, no beneficial effects were noted. Of the total 31 patients 25 patients, or 81 per cent, recovered in from 2 to 4 days without developing complications. Three patients, (10 per cent) showed definite improvement after two to four days, and although minor complications occurred during convalescence, they were discharged completely recovered. Three patients (10 per cent) were admitted in a moribund condition and died from streptococcus hemolyticus septicemia and pneumonia.

The average reduction in temperature, pulse rate and respiratory rate during the twelve hours following the serum injection was as follows: in temperature, 4.3 degrees; in pulse, 38 beats per minute, and in respirations, 8 per minute; in leucocytosis, 13,500 cells; the greatest reduction was 25,760 and the smallest 3140. The average general rash extinction time was 15 hours, the shortest time recorded was 9 hours and the longest time 36 hours.

Complications in order of frequency occurred as follows: septicemia in 2 cases, or 6 per cent; otitis media, pneumonia, pyelitis and arthritis, each

TABLE III

Comparison of clinical effects with therapeutic doses of convalescent scarlet fever serum and of Dochez' scarlatinal antistreptococci serum

	CONVALESCENT SERUM	DOCHEZ' SERUM
Total cases treated	37	31
Children	26	16
Adults	11	15
Nature of disease:		
Malignant	2	3
Severe	15	15
Moderately severe	15	11
Mild	5	2
Average dose (cc.)	20	40
Smallest dose (cc.)	15	10
Largest dose (cc.)	85	80
Average reduction within 12 hours in:		
Temperature	2.8°	4.3°
Pulse	16	38
Respirations	5	8
Leucocytosis	7,000	13,500
Time of general rash extinction (hours)	72	15
Results of treatment:		
Recovery without complications	35%	80%
Recovery with complications	59%	12%
Died	6%	9%
Complications:		
Cervical adenitis	19%	6%
Arthritis	19%	3%
Suppurating otitis media	13%	3%
Rhinitis	11%	0
Myocarditis	11%	0
Nephritis	8%	0
Endocarditis	5%	0
Pyelitis	5%	3%
Suppurating axillary abscesses	5%	0
Septicemia	5%	6%
Lobar pneumonia	3%	3%
Serum sickness	0	29%
Complete recovery without residua	77%	91%

in one case, or 3 per cent. Serum sickness occurred in 9 cases, or 29 per cent. No instance of nephritis developed in this series during an average stay in the hospital of twenty-two days after the onset of the

disease. Reëxamination of these patients, four to six months after discharge from the hospital, revealed no post-scarlatinal sequelae.

Brief case reports of 8 cases treated with Dochez' serum follow:

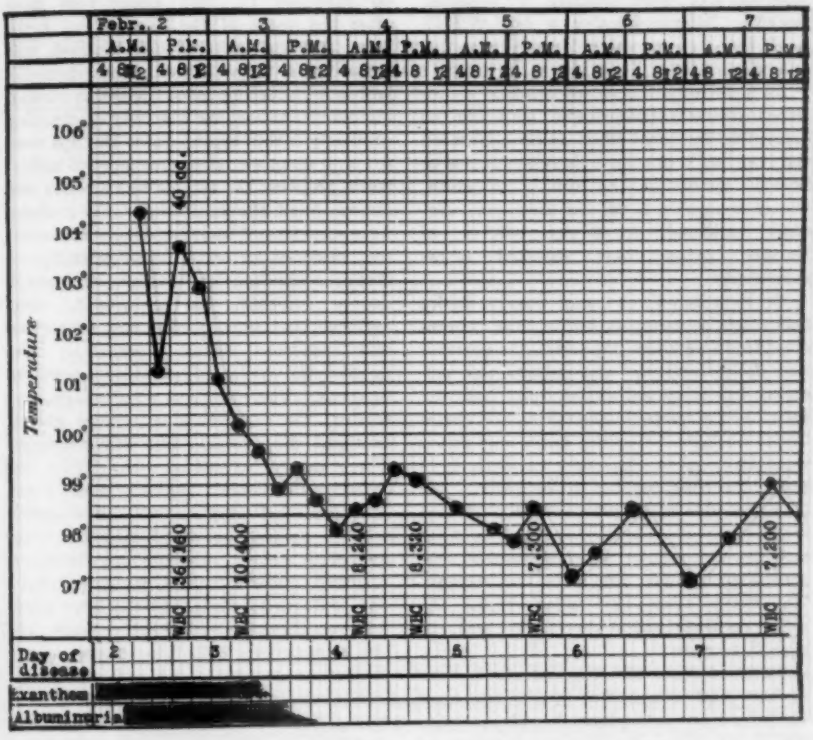

FIG. 4. COURSE OF TEMPERATURE IN CASE 1, ADMITTED ON SECOND DAY OF SCARLET FEVER

Case 1. M. B., schoolgirl, aged 9, admitted to the Sydenham Hospital on February 2, 1924, about forty hours after the appearance of the rash and on the second day of the disease. She was very drowsy, disoriented and semi-delirious. The face was flushed; the conjunctivae were injected and discharging a mucopurulent fluid; the lips were dry, chapped and bleeding; the tongue was coated with a dense whitish furring and the papillae were prominent, while the edges of the tongue were swollen and deeply injected. The tonsils were large and strawberry-red in color, their mesial surfaces almost touched each other, pushing before them a large, swollen and deeply injected uvula. Numerous yellow-white exudative plaques were scattered over both tonsils and the uvula. The entire faucial ring showed a deeply injected mucous membrane, in which were noted numerous petechiae. The hands and feet were cold and cyanotic. There was an intense brick-red rash over the entire body, papular in type, with numerous miliary sudamina about the axillae and in the groin. Edema of the skin was marked in dependent portions of the back. The temperature was 103.6°;

the pulse, 130, and respirations, 30. Blood-culture sterile after 48 hours' incubation.

Examination of the blood: R.B.C., 4,736,000; Hb. 83 per cent, (Sahli); W.B.C., 36,160. Diff. count: P.M.N., 91 per cent; P.M.E., 5 per cent; Lymph., 3 per cent; Mon., 1 per cent. Platelets reduced.

Urine: deep amber in color; acid in reaction; S.G., 1020; albumin, +; urobilin, positive. Microscopically: a few W.B.C. no R.B.C.; an occasional finely granular and waxy cast.

At 1:30 p.m., 0.5 cc. of Dochez' serum was injected intradermally in order to determine the local effect of the serum on the rash; at 8:45 p.m. a definite blanching became visible at the site of injection, which measured 5 cm. in diameter, regularly outlined. At 9 p.m., 40 cc. of Dochez' serum were injected intramuscularly.

On February 3, at 9 a.m. (twelve hours following the serum injection), the general condition was much improved; the toxemia had diminished and the patient was oriented, talkative and sitting up in bed; the rash had completely faded from the entire body; on light palpation there was felt a punctate, papular elevation, particularly in the axillary regions and in the groin. The face was pale and the color of the mucous membranes of normal hue; the cervical angina was greatly diminished and the tonsils and faucial ring were less swollen. The temperature had fallen during the night to 99.8°; the pulse to 80, and the respirations to 24.

Examination of the blood: W.B.C. 10,400. Diff. count: P.M.N., 78 per cent; P.M.E., 3 per cent; Lymph., 17 per cent; Trans., 2 per cent. Marked increase in platelets.

On February 4, the patient's condition was decidedly improved; she was playful and alert. The tonsils were diminished in size; the angina had entirely disappeared. There was a definite indication of pin-point-sized desquamation about the axillary regions and in the groin. Temperature, pulse and respiration normal.

Examination of the blood: W.B.C., 8,240. Diff. count; P.M.N., 79 per cent; P.M.E., 3 per cent; Lymph., 15 per cent; Monos., 1 per cent; Trans., 2 per cent.

Urine: Acid; S.G., 1016; albumin 0; urobilin 0. Microscopically: a few W.B.C.; no casts; no R.B.C.

No complications developed and the patient remained in excellent condition.

Case 2. D. G., factory superintendent, aged 33, admitted to the Sydenham Hospital on February 11, 1924, about four days after the onset of the disease and three days after the appearance of the rash, was found to be very ill, talking incoherently and in a muttering tone; there was marked circumoral pallor; the nose was discharging profusely a thin serous fluid; the lips were dry and chapped; the gums showed milky-white patches; the tongue was swollen and almost filled the oral cavity, its surfaces were smooth and its color deep strawberry-red, raw-looking and studded with hypertrophied papillae; the tonsils were small, deeply injected, having glazed, clean surfaces; the faucial ring was edematous and numerous definite petechiae were noted in the uvula, soft palate and posterior pharynx. The neck was swollen and very tender; the cervical glands were greatly enlarged, discrete and firm in consistence. There was an extensive rash, evenly and diffusely distributed over the neck, chest, abdomen and thighs, with innumerable miliary vesicles scattered over the trunk and thigh, conical in shape and containing a turbid, yellowish fluid, which yielded a pure culture of Streptococcus beta hemolyticus. Temperature 103.0°; pulse 110; the respirations, 34. The blood culture yielded no growth.

Examination of the blood: R.B.C., 5,012,000; Hb., 95 per cent (Sahli); W.B.C., 24,400.

Diff. count: P.M.N., 86 per cent; P.M.E., 0 per cent; P.M.B., 0 per cent; Lymph., 5 per cent; Monos., 3 per cent; Trans., 6 per cent. Platelets decreased.

Urine: Acid; S.G., 1031; albumin, ++; urobilin, strongly positive. Microscopically: a few W.B.C.; many waxy and granular casts. Numerous R.B.C. (guaiac, strongly positive).

At 9:50 p.m., 40 cc. of Dochez' serum were injected intramuscularly, following a previous positive blanching-test with 0.5 cc. of the serum.

On February 12, at 11 a.m. (thirteen hours following serum injection), the general condition was distinctly improved; the toxemic manifestations had abated and the patient expressed himself as "feeling much brighter and happier." His conversation was rational. The face and neck were less flushed and the conjunctivae were less injected and watery; the tongue was reduced in size, although still excoriated; the cervical glands were still greatly swollen, but the angina was somewhat improved. The diffuse rash was decidedly reduced in intensity and now appeared as dusky rose-red over the trunk and thighs. An unusual area of blanching was noted about the site of injection of the therapeutic dose of serum, regularly outlined, measuring 12 cm. in diameter; the initial blanched area, following upon the intradermal injection of 0.5 cc. of the serum, had now assumed a deep strawberry-red color, delimited exactly within the first area of rash extinction. The temperature had fallen to 98.6°; the pulse to 88; and the respirations to 18.

Examination of the blood: W.B.C., 11,150; Diff. count: P.M.N., 78 per cent; P.M.E., 2 per cent; Lymph., 14 per cent; Monos., 2 per cent; Trans., 2 per cent. Platelets normal in numbers.

On February 13, the patient appeared comfortable and cheerful, taking a lively interest in his surroundings and anxious to get out of bed. The edema of the tongue and the soreness of the throat had disappeared and the cervical angina was almost entirely relieved. The dusky-red

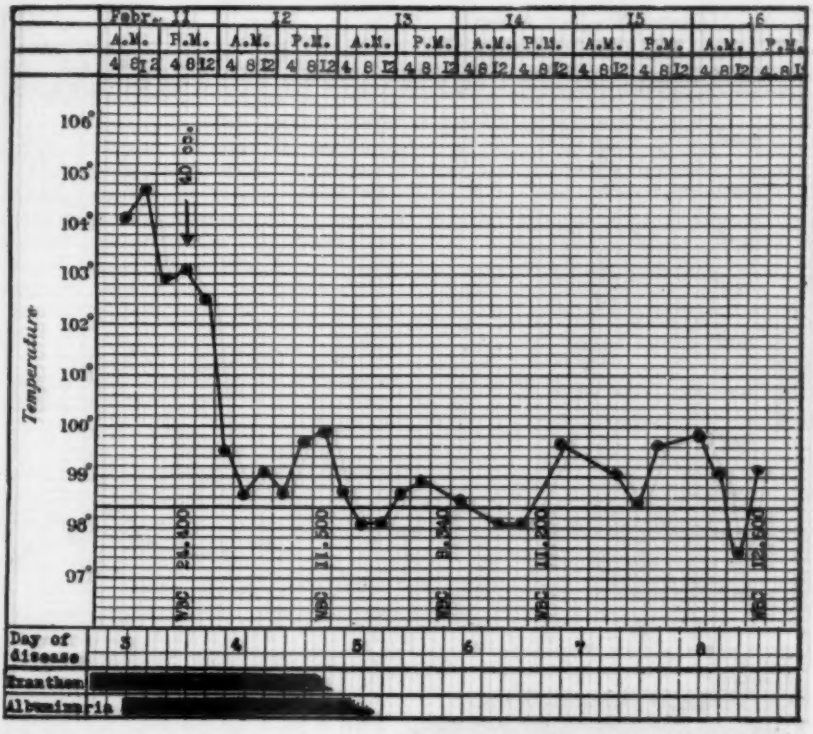

FIG. 5. COURSE OF TEMPERATURE IN CASE 2, ADMITTED ON THIRD DAY OF SCARLET FEVER

rash had faded and desquamation was in full progress on the trunk and extremities. Temperature, pulse and respiration normal.

Examination of the blood: W.B.C., 11,150. Diff. count: P.M.N., 78 per cent; P.M.E., 2 per cent; Lymph., 14 per cent; Monos., 2 per cent; Trans., 2 per cent; Platelets normal in numbers.

On February 13, the patient appeared comfortable and cheerful, taking a lively interest in his surroundings and eager to get out of bed. The edema of the tongue and the soreness of the throat had disappeared and the cervical angina was almost entirely relieved. The dusky-red rash had faded and desquamation was in full progress on the trunk and extremities. Temperature, pulse and respiration normal.

Examination of the blood: W.B.C., 8340. Diff. count: P.M.N., 73 per cent; P.M.E., 1 per cent; Lymph., 18 per cent; Monos., 6 per cent; Trans., 2 per cent. Platelets normal.

Urine: Acid; S.G., 1019; albumin 0; urobilin 0; guaiac 0. Microscopically: No casts; a few W.B.C.; no R.B.C.

On February 14, the patient developed a left otitis media and paracentesis was performed; a turbid, serous discharge

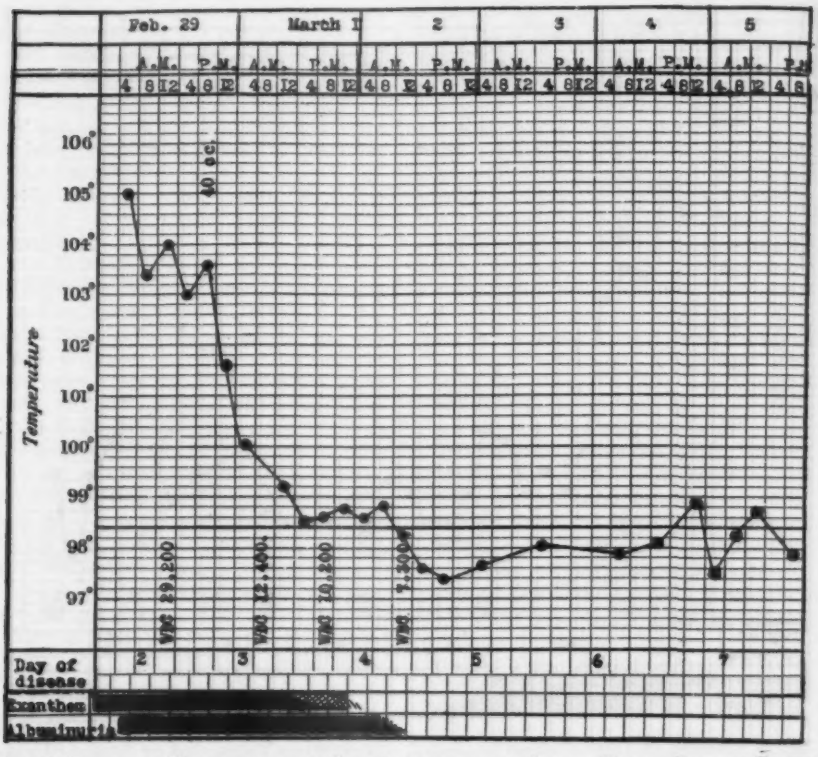

FIG. 6. COURSE OF TEMPERATURE IN CASE 3, ADMITTED ON SECOND DAY OF SCARLET FEVER

yielded Streptococcus beta hemolyticus and Staphylococcus aureus.

The left ear discharged a serous fluid for three weeks. Otherwise the patient remained in good health and without other complications.

Case 3. A. N., nurse, aged 39, admitted to the Sydenham Hospital on February 29,

1924, about forty hours after the appearance of the rash and on the second day of the disease, appeared to be very ill. The face was flushed; the tongue was swollen and deeply injected and the papillae were prominent; the tonsils were enlarged and presented numerous white plaques of exudate. The cervical glands were much enlarged and very tender. There was a scarlet blush over the entire body and numerous small hemorrhages in the axillary folds. The skin was edematous over the dependent portions of the back. Temperature, 103.4°; pulse, 124; the respirations, 32. The blood-culture was sterile.

Examination of the blood: W.B.C., 29,200. Diff. count: P.M.N., 93 per cent; P.M.E., 2 per cent; P.M.B., 0 per cent; Lymph., 5 per cent; Monos., 0 per cent. Platelets greatly reduced.

Urine: dark brown and turbid; acid in reaction; S.G., 1019; albumin, ++; urobilin strongly positive. Microscopically: numerous coarse granular casts; a few W.B.C. No R.B.C.

At 1 p.m., 0.5 cc. of Dochez' serum was injected intradermally. At 8:30 p.m. a definite rash extinction took place at the site of the injection of the serum, measuring about 3 cm. in diameter, showing very irregular edges and extending farthest along the lymphatics. At 9:10 p.m., 40 cc. of Dochez' serum were injected intramuscularly. The temperature was 103.6°; the pulse, 136; respirations, 38.

On March 1, 8 a.m. (eleven hours following serum injection) there was a striking clinical change in the patient's condition; the manifestations of toxemia had disappeared and she was mentally alert and cooperative. The angina was noticeably relieved and there was no trace of membrane on either tonsil. The diffuse and almost purplish exanthem had faded from the trunk and arms, though the legs, dependent portions of the back and the perineum remained vividly red. The temperature had fallen to 98.4°, the pulse to 84 and respirations to 22.

Examination of the blood: W.B.C., 10,200. Diff. count: P.M.N., 78 per cent; P.M.E., 5 per cent; P.M.B., 0 per cent; Lymph., 16 per cent; Monos., 1 per cent. Platelets slightly reduced.

The urine was acid in reaction, straw-colored and clear; S.G., 1016; trace of albumin; urobilin slightly positive; no cylindruria.

On March 2, the patient's general condition was good; the throat was not remarkable and the rash had completely faded except for small residual areas over the buttocks.

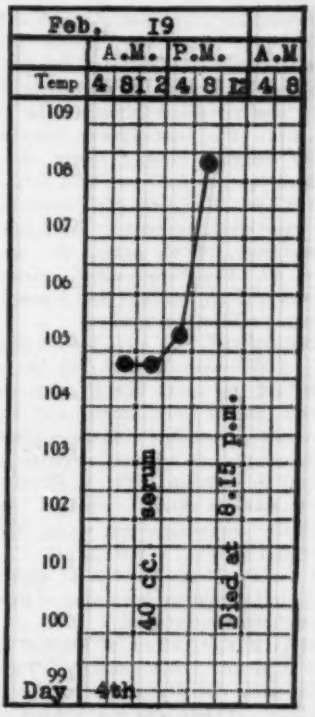

Fig. 7. Course of Temperature in Case 4, Admitted on Fourth Day of Scarlet Fever

The blood showed W.B.C. 7300. The urine was essentially negative.

On March 6 serum sickness developed and was severe for three days. The patient has since remained well, having developed no septic complications.

Case 4. R. F., schoolboy, aged 10, was admitted to the Sydenham Hospital on

February 19, 1924, four days after the appearance of the rash, in a moribund condition, showing profound toxemia and deep cyanosis. The face was not flushed, but rather pallid, and circumoral shadows were pronounced. The conjunctivae were injected, and discharged a thick purulent material. The right ear-drum was ruptured and a thin serous fluid was freely draining from the ear. The oral cavity showed an extreme degree of sepsis and the tonsils were completely covered with a greenish-white pultaceous membrane, which extended down the pharynx. There was a dusky-red erythema on the trunk and over the extremities. Inspiratory stridor became rapidly worse so that tracheotomy was indicated and performed at 7:10 a.m. The patient's general condition was slightly relieved by this operation. Temperature, 104.8°; pulse, 150; respirations, 50. The blood-culture yielded 4 colonies of Streptococcus beta hemolyticus per cubic centimeter of blood.

Examination of the blood: W.B.C., 7200. Diff. count: P.M.N., 65 per cent; P.M.E., 0 per cent; P.M.B., 0 per cent; Lymph., 28 per cent; Monos. and Trans., 6 per cent. Complete absence of platelets.

The urine was murky brown in color; neutral in reaction; S.G., 1028; albumin, +++; urobilin, strongly positive. Microscopically: abundance of waxy, cellular casts and W.B.C.; a few R.B.C.

A throat culture yielded no diphtheria bacilli but innumerable colonies of Streptococcus beta hemolyticus.

At 11:20 a.m., 35 cc. of Dochez' serum were injected intramuscularly. The condition grew rapidly worse and cyanosis deepened. There was no abatement in temperature, which at 6 p.m. rose to 108°. The patient died at 8:50 p.m.

Case 5. J. W., schoolboy, aged 14, when admitted to the Sydenham Hospital on April 26, 1924, about fifty hours after the initial appearance of the rash, was drowsy and presented the appearance of moderate toxemia. He was continually moaning in a low voice, complaining of "sweltering headache, sore throat and itching all over." The face was swollen, deeply red, hot, dry and scaly. The conjunctivae were injected, and discharged a thick, serous fluid. The nose was crusted and the nares obstructed by a thick, muco-purulent discharge. The tongue was swollen and brawny in appearance; the tonsils were prominent and projected into the faucial ring in such a manner as to obstruct the pharyngeal passage, necessitating a gulping movement during every respiratory phase. The glands at the angle of the jaw were much enlarged, firm and tender. The chest and abdomen were essentially negative. There was an intense scarlatinal rash on the trunk and extremities, with pitting edema over the dependent portions of the back. Sensorium distinctly clouded. Temperature, 102.1°; pulse, 110; and respirations, 24.

On April 27, at 10 a.m., the patient's general condition was much worse. Nausea, vomiting and chills developed and deep cyanosis was noted on the hands and feet. Temperature, 102.4°; pulse, 134; respirations, 28.

Examination of the blood: R.B.C., 4,936,000; W.B.C., 26,200; Hb., 95 per cent (Sahli). Diff. count: P.M.N., 91 per cent; P.M.E., 1 per cent; Lymph., 4 per cent; Trans., 2 per cent; Myelocytes, 2 per cent. Platelets conspicuously absent.

The urine was dark, cloudy and amber in color; acid in reaction; S.G., 1027; albumin, ++; urobilin, strongly positive. Microscopically: many coarse, cellular casts; a few W.B.C. and R.B.C. (guaiac slightly positive).

At 10:15 a.m., 40 cc. of Dochez' serum were injected intramuscularly. At 2 p.m., there was some clinical improvement in the patient's general condition; he was resting quietly, talked frequently with the nurse and seemed mentally clearer.

At 11 p.m. (thirteen hours after the injection of serum) the rash had almost completely faded, except over the gluteal regions. The pulse, temperature and respiration were normal. The angina was slightly improved and swallowing was less painful.

April 28, 8 a.m., the rash had completely faded, the patient was alert, talkative and expressed himself as "feeling fine." The tonsils were still greatly enlarged and protruding. The cervical glands were small

in size and slightly tender. Movements of the neck were painful.

Examination of the blood: W.B.C., 12,000. Diff. count: P.M.N., 75 per cent; P.M.E., 2 per cent; Lymph., 19 per cent; Monos. and Trans., 4 per cent. No myelocytes. Platelets increasing in numbers.

Urine: dark amber in color; acid in reaction; S.G., 1021; albumin negative; urobilin negative. Microscopically: no casts or W.B.C.; numerous epithelial cells.

The blood-culture taken on admission, yielded no growth of bacteria after 48 hours' incubation.

On April 29, 8 a.m., multiple arthritis had developed, mainly in the smaller joints. The temperature and pulse were elevated.

On May 1, the patient was distressed by the arthralgia, which mainly affected the smaller joints in the hands and feet. Salicylates gave some relief. The faucial ring was normal in appearance, except for greatly hypertrophied and cryptic tonsils. Serum sickness developed.

On May 5 the patient appeared well. During the last twenty-four hours there had been no arthralgia and the serum sickness had cleared up. No glandular enlargement was noted. No further complications developed and the patient recovered completely.

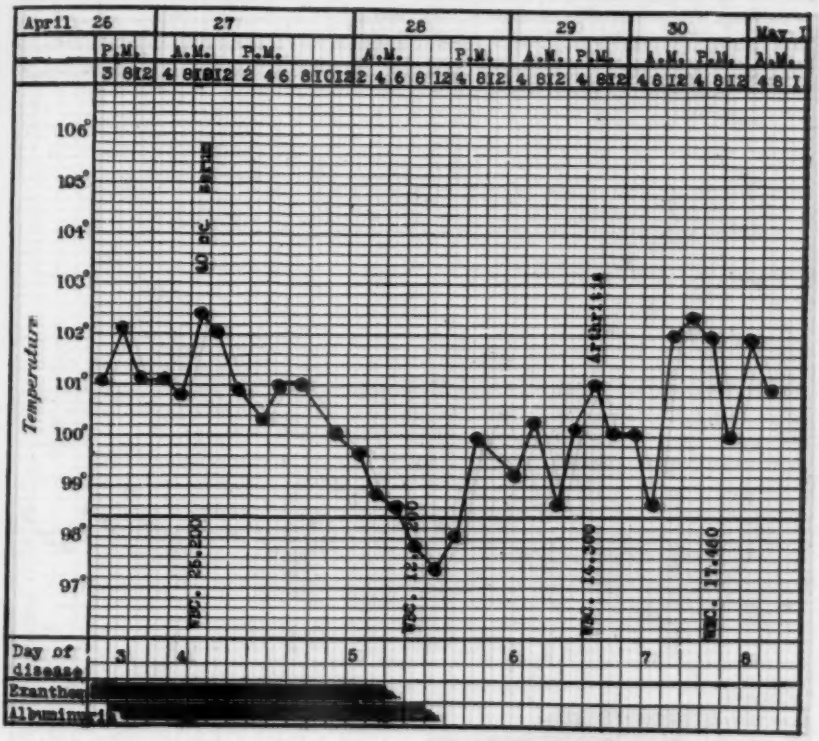

FIG. 8. COURSE OF TEMPERATURE IN CASE 5, ADMITTED ON THIRD DAY OF SCARLET FEVER

Case 6. C. L., engineer, aged 25, admitted to the Sydenham Hospital on April 28, 1924, about fourteen hours after the appearance of the rash. He was very ill. The face was vividly flushed and circumoral

pallor was marked. The lips were thick, dry and chapped; the tongue was furred and brown in the center. The edges swollen and strawberry-red in color; the tonsils were enlarged, deeply injected and covered with a yellowish-brown membrane, which extended across the junctions of the uvula, towards the soft palate. Numerous large petechiae were seen in the faucial ring and the posterior pharynx. The cervical glands were enlarged, discrete, firm and tender. Edema of the neck was pronounced. There was an intense brick-red rash, finely papular, on arms trunk and thighs. The patient complained of severe, general pruritus and frontal headache. Temperature, 104.4°; pulse, 128; respirations, 30.

Examination of the blood: R.B.C., 5,326,000; Hb. 96 per cent (Sahli); W.B.C., 22,300. Diff. count: P.M.N., 86 per cent; P.M.E., 0 per cent; Lymph., 5 per cent; Monos., 4 per cent; Myelocytes, 5 per cent. Platelets decreased.

Urine: cloudy pink in color; alkaline in reaction; S.G., 1022; albumin, ++; urobilin, strongly positive. Microscopically: many finely granular and cellular casts, W.B.C. and R.B.C. Guaiac, positive. The blood culture was sterile after 48 hours' incubation.

At 10:10 p.m., 60 cc. of Dochez' serum were given intramuscularly.

On April 29, at 12 noon (fourteen hours after the serum injection) the patient's

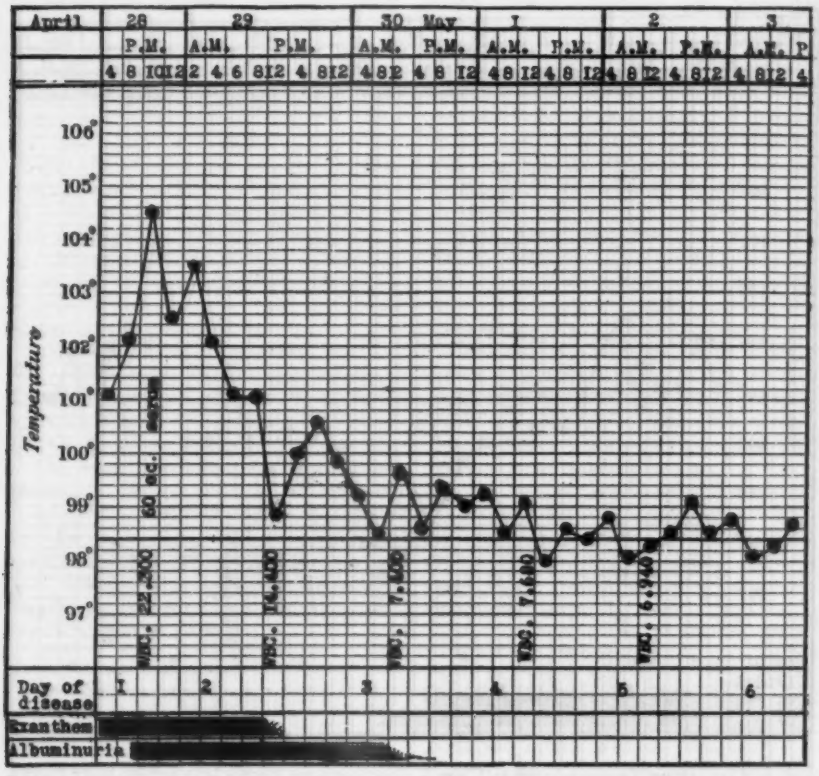

FIG. 9. COURSE OF TEMPERATURE IN CASE 6, ADMITTED ON FIRST DAY OF SCARLET FEVER

general condition was considerably improved. He was mentally cooperative and alert and commented on his sudden improvement. The rash had completely disappeared. The temperature had fallen to 98.8°; the pulse to 100 and respirations to 16. The swelling of the faucial ring was still marked and very painful.

Examination of the blood: W.B.C., 14,000. Diff. count: P.M.N., 65 per cent; P.M.E., 4 per cent, P.M.B., 0 per cent; Lymph., 17 per cent; Monos., 11 per cent; Trans., 3 per cent. No myelocytes. Platelets normal in number.

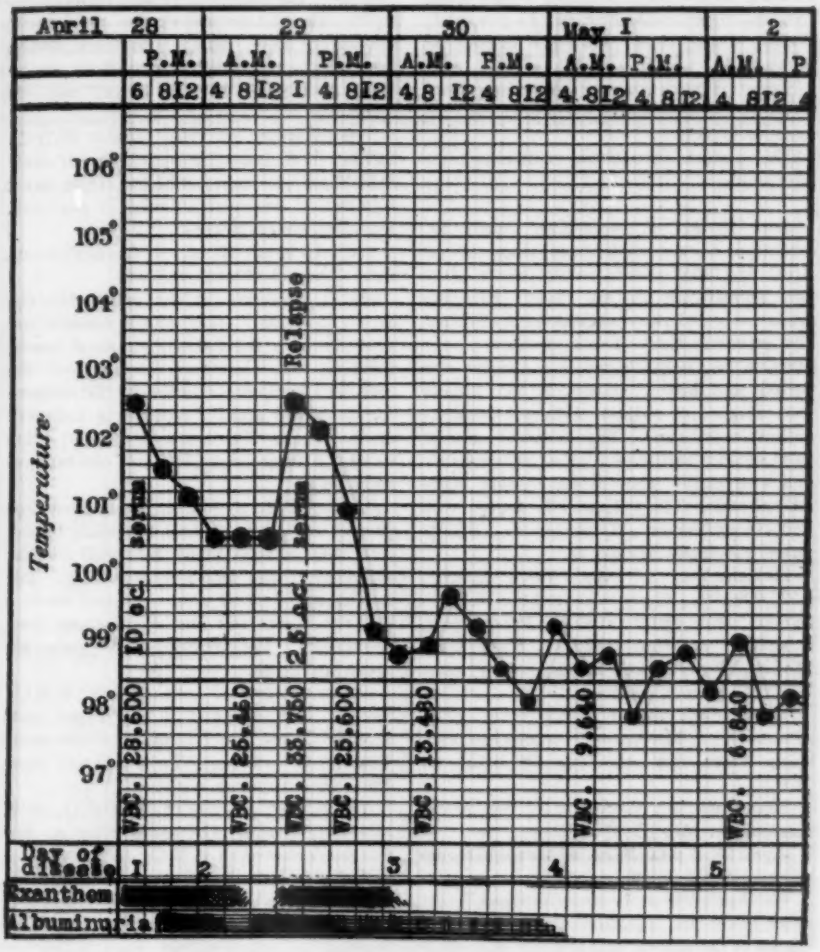

FIG. 10. COURSE OF TEMPERATURE IN CASE 7, ADMITTED ON FIRST DAY OF SCARLET FEVER

On April 30, the patient appeared well and attempted to sit up in bed and read. His mental status was normal. The tonsils were slightly enlarged, but free from membrane and not strikingly injected. Swallowing was not painful. The rash had

completely faded except for a brownish pigmentation on the arms, trunk and thigh.

Examination of the blood: W.B.C., 7400. Diff. count: P.M.N., 66 per cent; P.M.E., 4 per cent; P.M.B., 1 per cent; Lymph., 9 per cent; Monos., 16 per cent; Trans., 4 per cent. Platelets normal in numbers.

Urine: clear, straw-colored; alkaline; S.G., 1018; albumin, 0; urobilin, 0. No casts or W.B.C.

The patient recovered without complications.

Case 7. M. S., schoolboy, aged 10, admitted to the Sydenham Hospital on April 28, 1924, about twenty hours after the appearance of the rash. He was moderately sick; the face was deeply flushed and swollen; there was a profuse mucopurulent nasal discharge; the tongue was furred and heavily injected; the tonsils were large and covered with a brownish-yellow membrane. The cervical glands were swollen and tender. The entire trunk and extremities showed an intense scarlatinal rash. The patient was drowsy and had incontinence. Temperature, 102.4°; pulse, 116, respirations, 28.

Examination of the blood: R.B.C., 4,237,000; Hb., 84 per cent (Sahli); W.B.C., 28,600. Diff. count: P.M.N., 89 per cent; P.M.E., 1 per cent; Lymph., 3 per cent; Monos., 7 per cent; Trans., 0 per cent. Platelets greatly reduced.

Urine: dark amber; acid; S.G., 1025; albumin +. Microscopic: numerous fine, waxy casts; an occasional W.B.C.; no R.B.C.

Blood culture sterile after 48 hours' incubation.

April 28, 6 p.m. 10 cc. of Dochez' serum were injected intramuscularly.

On April 29, at 8 a.m. (fourteen hours after the serum injection) the general condition of the patient was slightly improved; the toxic symptoms had cleared up and he no longer voided involuntarily; the rash had almost disappeared, except over the back. Temperature, 100.6°; pulse, 98; respirations, 24.

Examination of the blood: W.B.C., 25,400. Diff. count: P.M.N., 83 per cent; P.M.E., 0 per cent; P.M.B., 2 per cent; Lymph., 6 per cent; Monos., 5 per cent; Trans., 2 per cent; Myelocytes, 2 per cent. Platelets greatly reduced.

At 1 p.m. the temperature suddenly rose to 102.6°; the pulse to 160, and respirations to 36. He had several chills. An intense scarlatinal rash, which was much deeper in color than the rash observed on admission, developed over the trunk and extremities.

Examination of the blood: W.B.C., 33,750. Diff. count: P.M.N., 86 per cent; P.M.E., 2 per cent; P.M.B., 0 per cent; Lymph., 11 per cent; Monos., 1 per cent. Platelets almost absent.

At 1:10 p.m., 25 cc. of Dochez' serum were injected intramuscularly.

At 12 midnight (eleven hours after the serum injection) there was a distinct improvement in the patient's general condition; he was alert and cooperative; the rash had completely faded in the extremities and was greatly reduced in intensity on the trunk. The temperature had fallen to 99.0°; the pulse to 110, and the respirations to 24.

On April 30, at 8 a.m., the patient appeared well and was found reading in bed. The rash on the trunk was still visible, although it had faded considerably. The tonsils and faucial ring were less swollen and the membrane had disappeared from the tonsils. Temperature, 98.4°; pulse, 82; respirations, 20.

Examination of the blood: W.B.C., 13,480. Diff. count: P.M.N., 77 per cent; P.M.E., 0 per cent; Lymph., 9 per cent; Monos., 12 per cent; Trans., 2 per cent. Platelets normal in numbers.

Urine: deep amber; alkaline; S.G., 1019; albumin, trace. Microscopically: a few fine waxy casts and W.B.C.; no R.B.C.

On May 1, the patient was sitting up in bed. The rash had completely faded and the faucial ring and both tonsils appeared normal.

He made an uneventful recovery.

Case 8. F. B., a boy, aged 5, admitted to the Sydenham Hospital on May 2, 1924, about twelve hours after the initial appearance of the rash, appeared very ill. The face was flushed; the conjunctivae were injected; the lips were dry and chapped;

the tongue was swollen and excoriated; the tonsils and faucial ring were swollen and numerous patches of white membrane were seen on both tonsils. The cervical glands were large, discrete and tender.

At 4 p.m., the general condition became worse; the rash deepened in intensity and numerous sudamina appeared about the axillae and over the thighs. The patient complained of headache and vomited twice

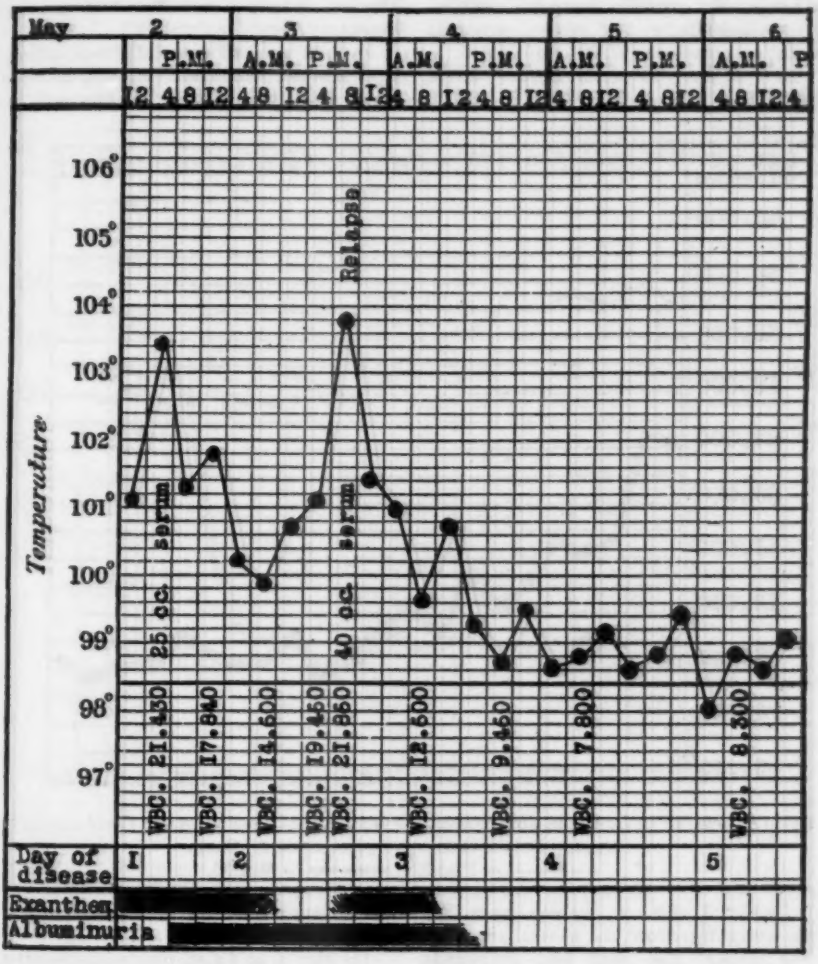

FIG. 11. COURSE OF TEMPERATURE IN CASE 8, ADMITTED ON FIRST DAY OF SCARLET FEVER

Loud systolic murmur at the apex of the heart. Bright red rash over the trunk and the extremities. Temperature, 101.1°; pulse, 128, respirations, 28.

within fifteen minutes. Temperature, 103.4°; pulse, 120, respirations, 28.

Examination of the blood: R.B.C., 4,645,000. Hb., 87 per cent (Sahli); W.B.C..

21,430. Diff. count: P.M.N., 91 per cent; P.M.E., 2 per cent; Lymph., 4 per cent; Monos., 1 per cent; Myelocytes, 2 per cent. Platelets decreased.

Urine: dark amber; acid; S.G. 1034; albumin, +; urobilin strongly positive. Microscopically: a few coarse, granular casts; an occasional W.B.C.; no R.B.C.

At 4:15 p.m., 25 cc. of Dochez' serum were given intramuscularly.

The rash reappeared over the neck, trunk and extremities and the angina increased.

Examination of the blood: W.B.C., 21,860. Diff. count: P.M.N., 91 per cent; P.M.E., 0 per cent; Lymph., 8 per cent; Monos., 1 per cent. Platelets almost absent.

At 8:35 p.m. 40 cc. of Dochez' serum were injected intramuscularly. At 12 midnight, there was a distinct improvement in

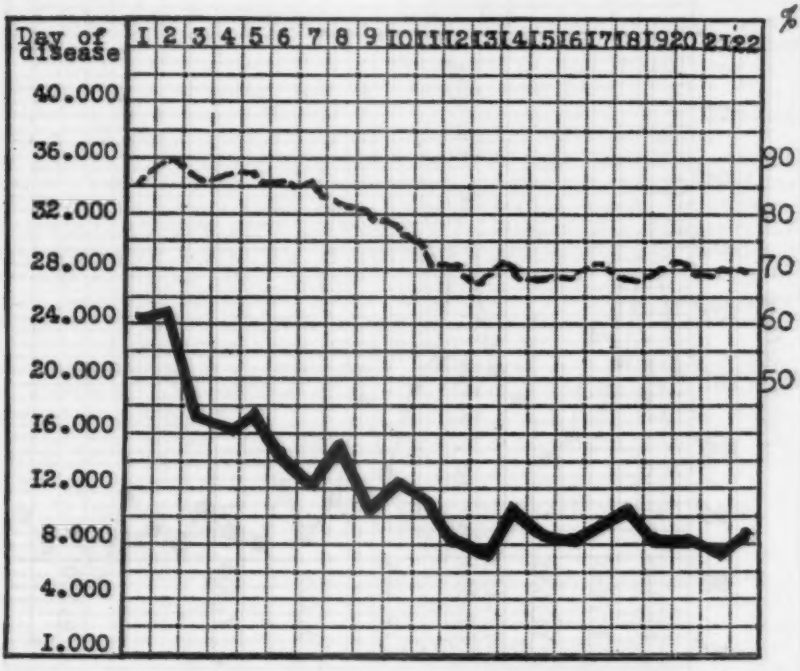

FIG. 12. LEUCOCYTE CURVE IN MODERATELY SEVERE CASES TREATED WITH CONVALESCENT SCARLET FEVER SERUM. AVERAGE OF 21 CASES
———— = P.M.N. ———— = W.B.C.

On May 3, at 8 a.m. (sixteen hours after the serum injection) the general condition was better. The rash had practically disappeared; the angina was less painful.

Examination of the blood: W.B.C., 14,600. Diff. count: P.M.N., 89 per cent; P.M.E., 2 per cent; Lymph., 4 per cent; Monos., 3 per cent; Trans., 2 per cent.

At 8 p.m., the patient had a chill and showed cyanosis of the hands and feet.

the patient's general condition and he was resting quietly.

On May 4, at 8 a.m. (twelve hours after the second injection of serum) the rash had faded, the patient appeared alert and talkative; the angina had diminished and swallowing of liquids was not particularly painful. Temperature, 99.6°; pulse, 98, respirations, 24.

Examination of the blood: W.B.C.,

12,600. Diff. count: P.M.N., 76 per cent; P.M.E., 5 per cent; Lymph., 17 per cent; Monos., 2 per cent.

On May 5, the patient was cheerful and active. The tonsils and faucial ring were less swollen and the membrane had disappeared. The cervical glands were small and only slightly tender.

Examination of the blood: W.B.C., 7,800. Diff. count: P.M.N., 87 per cent; P.M.E., 5 per cent; Lymph., 17 per cent; Monos., 0 per cent.

Urine: clear, amber; acid; S.G. 1018; albumin 0.

The patient recovered without complications.

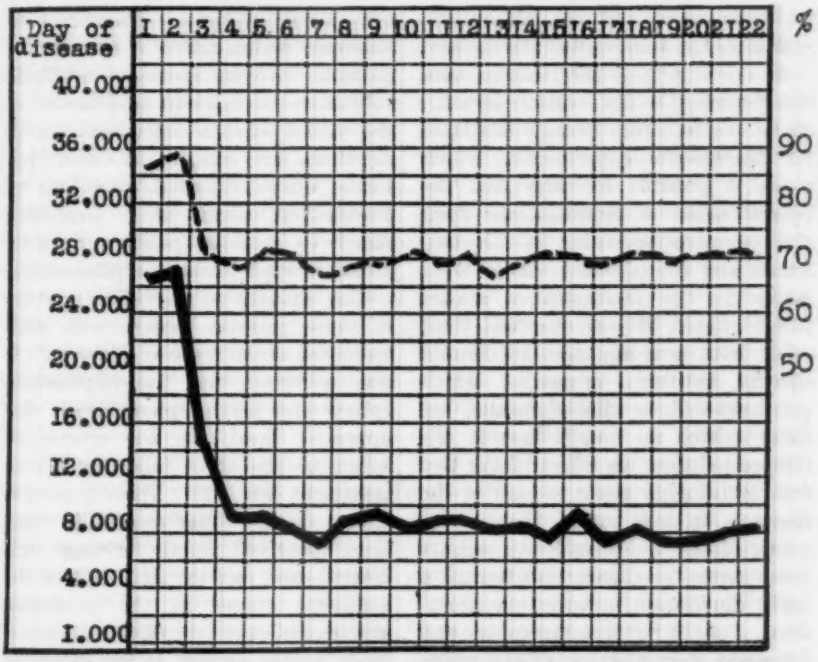

FIG. 13. LEUCOCYTE CURVE IN MODERATELY SEVERE CASES TREATED WITH DOCHEZ' SCARLATINAL ANTISTREPTOCOCCIC SERUM. AVERAGE OF 12 CASES

———— = P.M.N. ———— = W.B.C.

DISCUSSION

In a previous paper (22) dealing with the blanching phenomenon observed in scarlet fever patients tested with intradermal injections of normal human serum, convalescent scarlet fever serum, and Dochez' scarlatinal antistreptococcic serum, the author was able to demonstrate that there existed wide differences between the three sera as regards their specific blanching properties. It was noted that normal human serum produced the Schultz-Charlton rash extinction phenomenon in 56 per cent of scarlet fever rashes; convalescent scarlet fever serum caused blanching in 84 per cent, and Dochez' serum in 100 per cent. Further, it was apparent that Dochez' serum blanched in the same

patients a larger area of scarlet rash locally than did equivalent doses of either normal human serum or convalescent scarlet fever serum. It was also found that Dochez' serum continued to blanch the rash until the fourth day of the disease, after which time the results became irregular and inconclusive, while convalescent scarlet fever serum did not blanch the rash after the third day of the disease.

At the time these observations were being made, Dochez' scarlatinal antistreptococcic serum became available for therapeutic experiments, which made it possible to carry out the present series of investigations upon the comparative value of Dochez' serum and convalescent scarlet fever serum in the treatment of scarlet fever. Again, it was observed that, while both sera appeared to contain specific antitoxic properties which produced definite clinical results, yet there existed an unquestionable difference between the effect of the two sera in bringing about a cure of the disease. It was noted that therapeutic doses of convalescent scarlet fever serum produced consistently a rapid diminution in toxic manifestations, a slight fall in temperature and increased strengthening of the pulse. It was not apparent, however, that treatment with convalescent serum hastened convalescence, affected the duration of the general exanthem, or averted the usual incidence of septic complications that follow a severe attack of scarlet fever. Repeated doses of serum, administered to patients that did not respond favorably to the first injection, failed to effect a definite cure within a shorter period than that observed in untreated cases. This observation seemed to indicate that after a certain duration of the disease, the toxic substances produced in scarlet fever were definitely fixed in the tissues, and were not readily neutralized by the low concentration of antitoxic bodies contained in the convalescent scarlet fever serum. It was demonstrated repeatedly that even large therapeutic doses of convalescent serum failed to furnish the patients with an excess of antitoxic substance sufficient to be detected in the blood stream after the serum injection, for samples of these patients' serum collected from four to twenty-four hours after treatment failed to produce positive Schultz-Charlton rash extinction phenomena.

The changes in the blood picture in these patients treated with convalescent serum were of interest. It was observed that the hyperleucocytosis and polymorphonucleosis disappeared slowly in the course of seven to ten days following serum treatment (Fig. 12). These leucocyte curves do not differ materially from those observed in the average untreated case, and the similarity of the leucocyte curves in the untreated and treated cases (convalescent serum) lends further support to the idea that convalescent serum furnishes the patient with comparatively little antitoxic substance. In the untreated case of scarlet fever the decrease in leucocytes takes place at about the same time as the blood serum from these cases first begins to give the blanching phenomenon. The two processes seem to be coexistent with the formation of an excess of antitoxin in the circulating blood. The fact that the leucocytes of the cases treated

with convalescent serum followed the same curve as they did in the untreated cases, suggests that the production or appearance of an excess of antitoxin was no greater and did not take place any sooner in the treated than in the untreated cases. We are forced, therefore, to conclude that although therapeutic doses of convalescent scarlet fever serum improve the patient's general toxic depression and reduce temperature and pulse rate slightly, such doses do not contain sufficient concentration of antitoxic substances to bring about a definite cure in severe types of the disease or to prevent scarlatinal complications. Albuminuria and cylindruria persist in these cases, and the recovery, which is accompanied by an adenopathy, is slow. Unquestionably, however, the convalescent scarlet fever serum has a temporary effect upon the toxaemia, the temperature, and pulse rate.

The clinical effect obtained by the use of Dochez' scarlatinal antistreptococcic serum appears most favorable, perhaps, when contrasted with the therapeutic value of convalescent scarlet fever serum. An average therapeutic dose of 40 cc. of Dochez' serum brought about, with great regularity, a prompt disappearance of the toxaemia and a critical fall in temperature and pulse rate. The temperature invariably reached normal within eight to twelve hours after the administration of serum. The sudden disappearance of the general rash was quite as striking as the fall in temperature. This occurred irrespective of its original intensity. The earliest fading of the exanthem was observed seven hours after the serum injection and the longest period between the injection of serum and the disappearance of the rash was thirty-six hours. The adenopathy promptly subsided and the lymph nodes resumed their normal size simultaneously with the disappearance of albuminuria and cylindruria.

The blood-picture of the patients treated with Dochez' serum proved to be an index of the action of the serum, for it was found that the hyperleucocytosis and polymorphonucleosis decreased in a critical manner within twenty-four hours after the administration of serum. When the leucocytes had reached normal numbers, they remained throughout convalescence at this level.

That a dose of 40 cc. of Dochez' serum was adequate to neutralize completely the toxins produced in scarlet fever, was indicated by the rapid disappearance of toxaemia, by the prompt fading of the general rash and by the fact that an antitoxin was demonstrated in the circulating blood of the patients as early as six hours after the administration of the serum. Samples of the serum from these patients collected from six hours after treatment until their discharge from the hospital were found to produce positive Schultz-Charlton rash extinction phenomena. An insufficient dose of serum was clearly responsible for the sudden relapse which occurred in Cases 7 and 8; in these patients doses of 10 cc. and 25 cc. of serum were administered. In both instances the patients improved rapidly after the administration of serum, the temperature fell, the pulse rate slowed somewhat and the general rash faded. There was,

however, only a slight reduction in the leucocytosis. Samples of serum, collected hourly after the treatment, failed to produce the Schultz-Charlton rash extinction phenomenon. Relapse occurred in both patients with the return of the original symptoms, the rash being deeper in intensity than it was at the onset of the disease. A second dose of 25 cc. in one patient and 40 cc. in the other resulted in the prompt recovery of both patients without complications. The Schultz-Charlton phenomenon was obtained with the serum collected from these patients as early as eight hours after the second injection of serum.

The results following the use of Dochez' serum on patients who were admitted to the hospital after the fourth day of the disease, and in whom septic complications were already manifest, are as yet inconclusive. Patients treated during the first three days of the disease did not develop complications during their stay in the hospital. The incidence of complication rose rapidly in those admitted after the fourth day of the disease. In view of this fact, it is important to emphasize the necessity of administering the serum early. The high incidence of serum sickness is regrettable and it is hoped that this may be obviated by purification and higher concentration of the serum.

SUMMARY

In the study of 37 cases of scarlet fever treated by intramuscular injections of 15 to 85 cc. of serum from convalescent cases of scarlet fever, it was found that:

1. Convalescent scarlet fever serum causes a rapid improvement in the general symptoms and a slight fall in temperature and pulse rate, but produces no effect upon the general rash, and does not shorten the convalescence or reduce the incidence of septic complications during convalescence.

2. A comparative study of 31 cases of scarlet fever showed that the intramuscular injection of Dochez' scarlatinal antistreptococcic serum in amounts of 40 cc. administered during the first three days of the disease caused a prompt disappearance of the toxaemia, a critical fall in temperature and pulse rate, prompt fading of the general exanthem, rapid reduction in leucocytosis and rapid disappearance of the glandular enlargement.

3. The Schultz-Charlton rash extinction phenomenon can be obtained with samples of serum withdrawn from patients treated with Dochez' serum shortly after its injection.

4. A therapeutic dose of 40 cc. of Dochez' serum was sufficient to bring about a clinical cure in moderately severe cases of scarlet fever.

5. The incidence of septic complication was low in the cases treated with Dochez' serum prior to the fourth day of disease.

6. The cases presenting septic complications yielded slowly and irregularly to Dochez' serum.

The author wishes to acknowledge his indebtedness to Dr. A. L. Bloomfield for his assistance, to Dr. A. R. Dochez for the serum, and to Dr. Birkhead Macgowan for the privilege of making these studies at the Sydenham Hospital.

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Book Reviews

Sir William Osler Memorial Volume. Published under the auspices of the International Association of Medical Museums. Obtainable by subscription, $10.00 in advance, to Dr. Maude E. Abbott, 1300 Spruce Street, Philadelphia, Managing Editor.

This memorial volume, which will appear in April, 1925, contains some four hundred pages devoted to editorials and articles about Sir William Osler and many reminiscences of his early years and of his life and work at Montreal, Philadelphia, Baltimore and Oxford, which have been contributed by over ninety of his friends, associates and former students. In addition, there is a classified bibliography of Sir William Osler's contributions to medicine and also a bibliography of "Writings about Osler." The work of the volume was commenced in 1921, aided by a publication fund contributed by the National Research Council, Sir Edmund Osler, the Honorable Mr. Justice Featherstone Osler, Mrs. K. S. Reford, Mr. J. J. Carty and others. The volume is splendidly edited and illustrated.

W. C. D.

A Present-Day Conception of Mental Disorders. By C. M. CAMPBELL, M.D., 53 pp. $1.00. (*Harvard University Press, 1924.*)

This little volume is one of the series of Harvard Health Talks. Its contents are addressed particularly to the laity, but it presents a point of view which the medical profession will find stimulating and of value.

The author discusses the unfortunate shyness which exists towards the term "mental" and asks his readers to consider the topic, not as "mental disorders" but as "men, women and children in difficulty, suffering, hoping, thwarted, and groping." He then discusses the type of facts which are met with in mental disorders. These facts include the whole range of human behavior, from mild personality twists to profound disturbances involving the whole behavior of the individual. These facts are to be studied as problems of human nature working under difficulty, and the understanding of the facts comes only through studying the developmental history of the individual. He emphasizes that problems of mental disorders are the problems of human life and are different only in the degree and setting from the problems which all have to face.

The book is very readable and stimulating and incorporates the dynamic aspects of present-day psychiatry.

F. H. A.

The Evolution of Man. Essays. By G. ELLIOT SMITH. 159 pp. 8°. $2.85. (*Oxford University Press, American Branch, New York, 1924.*)

Three addresses are collected in this little book under the chapter headings: "Evolution of man," "Primitive man," and "Human brain." They are essays having as their subject in common the problem of man's origin and descent. In a foreword the author reviews our present knowledge and theories regarding the relations between the different genera and species of the human family and man's position among the Primates.

Much of the space is devoted to emphasizing the importance of the cultivation of vision, particularly the gradual acquisition of stereoscopic vision, in man's evolution. This theory is well known to those who had the pleasure of hearing the recent Herter lecture by the author. By this theory a new, and most convincing factor is added to (but does not replace) the older view that erect walk played the prominent rôle in man's emancipation from simian ancestors.

The delightful style, together with the stimulating and, at times, daring originality of the book, places it apart from the bulk of others dealing with the same general theme. However, the reader must keep constantly in mind the fact that many of the author's

speculations and deductions are valuable as suggestions and tentative working hypotheses rather than as well substantiated conclusions. It also must be noted that in referring to some of the controversies with which the history of finds of fossil man is so closely interwoven, the author has not dealt with the opposing views in quite an impartial manner.

A. H. S.

Radium Report of the Memorial Hospital. New York. [Second Series, 1923]. $5.00. (*New York. Paul B. Hoeber, Inc. 1924.*)

In this second series some eleven writers contribute their experiences in this new and ever growing science of radium therapy,—all the outgrowth of the large service and admirable opportunities of the Memorial Hospital.

The volume opens with two excellent papers, by the late greatly lamented H. H. Janeway, on the status and scope of radium therapy and the technical principles developed in the hospital. Upon reading these papers, one realizes anew how great is our loss in this bright, earnest, thorough scientist.

Beginning with Janeway, the paper ends happily with a fundamental philosophical paper by James Ewing, "An Analysis of Radium Therapy in Cancer," which ought to be read until all its data are mastered by every one who is engaged in this work. This was the Mütter lecture of the College of Physicians of Philadelphia, which should contribute to its wider distribution.

Douglas Quick writes admirably and with a clear grasp of his subject in a series of five papers, on intra-oral malignancy, on carcinoma of the rectum, new growths of the parotid, eyeball and orbit, and of the skin. Burton J. Lee, Harold Bailey, and Benjamin S. Barringer deal with breast, gynecological, and urinary cancers, respectively. William S. Stone, now a veteran in the field, discusses the scope of X-rays and radium.

The volume is well illustrated and full of interest to all who live daily in the presence of these newer difficult problems in the therapeutic world. No heartier appreciation can be expressed than the statement that we all look to the Memorial Hospital as a guide in these matters covering so large a field and calling for judgment often so difficult in view of the delicate physical problems involved, and complicated by the varying factors of manifold diseases, each with their differing age and individual susceptibilities,—where truly, as our Coan progenitor is declared to have said over two thousand years ago, "Judgment is difficult."

H. A. K.

The Internal Secretions. By Dr. Arthur Weil. Authorized Translation of the Third German Edition. By Jacob Gutman, M.D., $4.00 (*New York: The Macmillan Company*, 1924.)

Dr. Gutman has given an able and a pleasing translation of Weil's book on "The Internal Secretions," a book that had gone through three editions and had already been translated from the German into Spanish, Russian and Japanese.

The material is presented from the standpoint of the physiologist, and the method of presentation is interesting, in that the author has selected as subjects the important bodily functions and has described the way in which these functions are influenced by the endocrine glands. There are chapters, for instance, on the Circulation of the Blood, Respiration and Voice Production, Metabolism, Growth and Bodily Form, Reproduction, The Sexual Impulse and the Mind, and the Internal Secretions.

The book is small, its style attractive and an evening or two may be spent profitably in its perusal.

The author is obviously much interested in the glands of internal secretion and is perhaps somewhat prejudiced in favor of an incretory hypothesis in the explanation of phenomena that might be interpreted in other ways. He is, for example, less conservative than Bauer in his interpretation of the influence of the incretions upon growth and bodily form. He accepts the work and the opinions of Brown-Séquard and of Steinach upon the gonads and rejuvenation with little or no reservation. He sounds a note of warning, however, in the closing paragraphs of the book, that "the internal secretions are not an all-dominant force, but a force which shares the control of the life cycle with the brain and the autonomic nerve system."

F. P. L.

Lang's German-English Dictionary of Terms used in Medicine and the Allied Sciences. Edited and revised by MILTON K. MEYERS, M.D. 3rd edition, 1924, pp. 613. $7.00. *Philadelphia, P. Blackiston's Son & Co.*,

This excellent medical dictionary contains approximately 53,000 words and short, clear definitions of German medical terms, about 4000 new ones having been incorporated in the present new edition. German medical terms spelled exactly like their English equivalents have been omitted. Throughout; the modern German spelling has been employed, and the arrangement of the words should prove to be convenient. This work will, therefore, be very useful as an aid in the study of the vast German medical literature, so important for bringing about a closer association of medical people of English and German speaking countries.

In newer editions, it might be helpful if the reader were reminded in the preface that words begining with C, if not found under C, could probably be found under K or Z; that words beginning with ä, ö, ü should be looked up under ae, oe, ue. These suggestions appear in the present volume on p. 85 and p. 390, but are liable to be overlooked. If they were given a little more prominence, they would surely not be missed.

E. H.

Diseases of the Male Organs of Generation. By KENNETH M. WALKER, F.R.C.S. 234 pp. $4.00. Oxford Medical Publications. (*London, Henry Frowde and Hodder & Stoughton.*)

In this concise volume Walker discusses the diseases of the testicles, spermatic cord, prostate, seminal vesicles and external genitalia excluding, as far as possible, the diseases of the urinary tract and the venereal infections, although, of course, since they play a most important rôle, they have necessarily been dealt with, in so far as they affect the generative tract.

The book is primarily designed for the use of the student and the general practitioner and particular emphasis is laid upon medical treatment, minor surgery and the indications for major surgery. The major surgical operations are described briefly but sufficiently to give the reader a working knowledge of the correct procedures and the results to be expected after they have been intelligently executed.

In a book of this size it has naturally been impossible to consider pathological processes with any degree of thoroughness, and this subject is taken up only as far as is necessary to explain its bearing on treatment.

It is interesting to note that the author does not advise cystoscopic examination in cases of enlarged prostate unless there exist definite indications for this procedure. In most clinics in this country, a preliminary cystoscopy is done as a routine measure unless certain contraindications are present, as it is becoming more and more generally felt that the information which can be obtained from such an examination far outweighs the slight danger to the patient entailed by it.

It is surprising to find in the chapter on carcinoma of the prostate that no mention is made of the radical operation or of the palliative effect of a partial perineal prostatectomy in cases in which the growth has caused obstruction to urination.

The book can be unhesitatingly recommended to the student and to the practitioner who wishes to review the subject with special reference to treatment.

J. A. C. C.

The Endocrine Organs. An Introduction to the Study of Internal Secretions. By SIR E. SHARPEY-SCHAFER. Second Edition. Part 1. The Thyroid, the Parathyroids, and the Suprarenal Capsules. (*Longmans, Green & Co., London, 1924.*)

Part I of this work that deals with three of the endocrine glands is contained in a small, handy volume of 170 pages. The style is concise and readable. The material is presented chiefly from the standpoint of the physiologist with relatively brief references to clinical features. Sources of the more important or recent facts are indicated in footnotes.

Coming from a recognized and a conservative authority this book may be highly recommended as a safe guide to our present knowledge in this confusing domain of medicine.

T. P. S.